NHS England Evidence Review:

Ranibizumab for retinopathy of prematurity

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of ranibizumab compared to standard care for the treatment of retinopathy of prematurity (ROP) in preterm infants.

Preterm infants with ROP may include infants for whom laser treatment cannot be administered due to media opacity, equipment failure, small pupils or other factors, infants who are unstable and may not tolerate laser or sedation or infants for whom laser treatment has failed.

Ranibizumab is a vascular endothelial growth factor (VEGF) inhibitor. It is currently the only VEGF inhibitor licensed for ROP treatment in the UK. Intravitreal ranibizumab is administered as first line drug treatment. Patients may have received prior non-drug treatments.

Current standard care is diode laser treatment (retinal photocoagulation). In centres where diode laser equipment is not available, 2008 clinical guidelines recommended the use of cryotherapy or argon therapy. However, this guidance was revised in 2022[1]. An unlicensed alternative VEGF inhibitor, bevacizumab, is used in a few centres in England.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from ranibizumab more than others and the criteria used by the included studies to define those preterm infants diagnosed with ROP who are eligible to receive first line drug treatment with ranibizumab.

[1] In the UK 2022 ROP treatment guideline of the Royal College Ophthalmologists, cryotherapy is not recommended, and green wavelength laser (which includes Argon) is regarded as equivalent to diode laser (https://www.rcophth.ac.uk/resources-listing/uk-retinopathy-of-prematurity-guideline/)

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of ranibizumab compared to standard care for the treatment of retinopathy of prematurity (ROP) in preterm infants. The searches for evidence published since January 2012 were conducted on 18th March 2022 and identified 341 potential references. These were screened using their titles and abstracts and 25 full text papers potentially relating to the use of ranibizumab for ROP were obtained and assessed for relevance.

Seven studies (published in nine papers) were identified for inclusion, two randomised controlled trials (RCTs) and five retrospective cohort studies.

- The RAINBOW RCT (multi-centre (87 centres), 26 countries[2]) compared 0.2mg ranibizumab (n=74), 0.1mg ranibizumab (n=77) and laser therapy (n=74) in preterm infants with ROP. The RCT results with 24 weeks follow-up were reported in Stahl et al (2019) and results from a two-year interim analysis (n=153) from a five-year extension study[3] were published in Marlow et al (2021). A post-hoc subgroup analysis (n=225) of data from the RAINBOW RCT and extension study was published in Fleck et al (2022).
- The RCT by Zhang et al (2017) (single-centre, China) compared ranibizumab (n=25) and laser therapy (n=25) in preterm infants with ROP with at least six months follow-up.
- Two retrospective cohort studies from Poland and South Korea compared ranibizumab and laser therapy in preterm infants with ROP. Chmielarz-Czarnocińska et al (2021) compared ranibizumab (n=61) and laser therapy (n=115) with follow-up of up to six months. Kang et al (2019) (n=165) compared ranibizumab (153 eyes) and laser therapy (161 eyes) with a mean follow-up of 36.3 months.
- Two retrospective cohort studies from Turkey and Taiwan compared ranibizumab, laser therapy and bevacizumab in preterm infants with ROP. Gunay et al 2017 compared ranibizumab (n=22), laser therapy (n=57) and bevacizumab (n=55) with approximately 20 months follow-up. Ling et al (2020) (n=176) compared ranibizumab (48 eyes), laser therapy (61 eyes) and bevacizumab (231 eyes) with mean 197.3 weeks follow-up.
- One retrospective cohort study (Kang et al 2018) (n=83) from South Korea compared ranibizumab (52 eyes) and bevacizumab (101 eyes) in preterm infants with ROP with a mean follow-up of 13.9 months for ranibizumab and 30.9 months for bevacizumab.

No studies were identified comparing ranibizumab to cryotherapy or argon laser.

In terms of clinical effectiveness:

- **Unfavourable structural retinal outcomes (critical outcome).**
  - *For ranibizumab vs laser therapy:* One RCT provided low certainty evidence of unfavourable structural retinal outcomes in 1% and 7% of patients who received 0.2mg and 0.1mg of ranibizumab respectively and 10% of patients who received laser therapy after 24 weeks follow-up. The groups were not statistically compared. An extension study to this RCT provided low certainty evidence of no statistically significant difference in structural abnormalities between ranibizumab and laser therapy at age 20-28 months (corrected for prematurity). A second RCT reported no cases of retinal detachment with either ranibizumab or laser therapy at approximately 12 months follow-up. One retrospective cohort study provided very low certainty

[2] Japan (16 centres; 29 patients), US (12;21), India (6;29), Turkey (6;14), Russia (5;20), Italy (4;14), Austria (3;6), Czech Republic (3;9), Greece (3;10), Romania (3;16), UK (3;5), Belgium (2;10), Croatia (2;9), France (2;3), Germany (2;3), Hungary (2;2), Malaysia (2;2), Poland (2;3), Taiwan (2;7), Denmark (1;1), Egypt (1;3), Estonia (1;2), Lithuania (1;1), Mexico (1;6), Saudi Arabia (1;1), Slovakia (1;1)

[3] The final results of the five year extension study have not yet been published

evidence of statistically significantly fewer cases of retinal detachment and temporal dragging for ranibizumab compared to laser therapy at a mean of 36 months follow-up.
  - *For ranibizumab, laser therapy and bevacizumab:* One retrospective cohort study provided very low certainty evidence of no statistically significant difference in retinal detachment between ranibizumab, laser therapy and bevacizumab at a mean of 197 weeks follow-up. A second retrospective study provided very low certainty evidence of a single unfavourable anatomical outcome (1.8%) in a patient who received laser therapy and no cases with ranibizumab or bevacizumab at 18-20 months follow-up. The groups were not statistically compared.
  - *For ranibizumab vs bevacizumab:* One retrospective cohort study provided very low certainty evidence of no statistically significant difference in retinal detachment or temporal macular dragging between ranibizumab and bevacizumab at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab.

- **High myopia (critical outcome).**
  - *For ranibizumab vs laser therapy:* One RCT extension study provided low certainty evidence of statistically significantly less high myopia for 0.2mg ranibizumab compared to laser therapy at age 20-28 months (corrected for prematurity). There was no statistically significant difference in high myopia for 0.1mg ranibizumab compared to laser therapy in this study.
  - *For ranibizumab, laser therapy and bevacizumab:* One retrospective cohort study provided very low certainty evidence of no statistically significant difference in high myopia between ranibizumab, laser therapy and bevacizumab at approximately 18-20 months follow-up.

- **Sight impairment/ severe sight impairment[4] (critical outcome).**
  - *For ranibizumab vs laser therapy:* One RCT provided low certainty evidence of a single nystagmus case (1.4%) at 24 weeks follow-up for 0.2mg ranibizumab. There were no cases of nystagmus after 0.1mg ranibizumab or laser therapy. An extension study to this RCT provided low certainty evidence of outcomes at age 20-28 months (corrected for prematurity). This reported nystagmus in 3.6% and 6.0% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 12.2% after laser therapy. This study also reported strabismus in 20.0% and 24.5% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 31.7% after laser therapy. Abnormal fixation occurred in 1.8% and 15.4% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 14.5% after laser therapy. Abnormal pupil reaction occurred in 0% and 6.0% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 2.4% after laser therapy. This RCT and RCT extension study did not statistically compare the groups. One retrospective cohort study provided very low certainty evidence of no statistically significant difference in strabismus operations between ranibizumab and laser therapy at a mean of 36 months follow-up.
  - *For ranibizumab vs bevacizumab:* One retrospective cohort study provided very low certainty evidence of statistically significantly fewer strabismus operations for

[4] Conditions potentially relating to this outcome in the included studies were nystagmus, strabismus, abnormal fixation and abnormal pupil reaction. Nystagmus is a rhythmical, repetitive and involuntary movement of the eyes which the patient has no control over. There is no cure for nystagmus and sight problems are common (Nystagmus | Great Ormond Street Hospital (gosh.nhs.uk)). Strabismus is a squint, where the eyes point in different directions. If untreated in young children, lazy eye (amblyopia) can develop with poor vision in the eye with the squint (Squint (strabismus) - Moorfields Eye Hospital). However, it is also possible to have these conditions with normal or near normal vision. Abnormal fixation and abnormal pupil reaction were not further defined in the studies but may be associated with sight impairment/ severe sight impairment

ranibizumab compared to bevacizumab at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab.

- **Treatment failure[5] (important outcome).**
  - *For ranibizumab vs laser therapy:* One RCT provided low certainty evidence of treatment failure in 31% of patients with two different ranibizumab doses and 14% with laser therapy at up to 24 weeks follow-up. A second RCT provided low certainty evidence of treatment failure in 44% of patients with ranibizumab and 4% with laser therapy at up to approximately 12 months follow-up. The RCT groups were not statistically compared. One retrospective cohort study provided very low certainty evidence of no statistically significant difference in treatment failure between ranibizumab and laser therapy at approximately three years follow-up. A second retrospective cohort study provided very low certainty evidence of treatment failure in 67% of patients following ranibizumab and 0% of patients after laser therapy at up to six months follow-up. The groups were not statistically compared.
  - *For ranibizumab, laser therapy and bevacizumab:* Two retrospective cohort studies provided very low certainty evidence of no statistically significant difference in treatment failure between ranibizumab, laser therapy and bevacizumab at approximately three years and 18-20 months follow-up respectively. However, in one of these studies, treatment failure was statistically significantly higher for ranibizumab compared to bevacizumab in multivariable regression analysis.
  - *For ranibizumab vs bevacizumab:* One retrospective cohort study provided very low certainty evidence of treatment failure requiring any retreatment in 14% of patients after ranibizumab and 8% after bevacizumab at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab. This study also reported that statistically significantly more eyes initially treated with ranibizumab required retreatment with anti-VEGF compared to eyes initially treated with bevacizumab.

- **Quality of life (important outcome).**
  - *For ranibizumab vs laser therapy:* One RCT extension study provided low certainty evidence of no statistically significant difference in vision-related quality of life at age 20-28 months (corrected for prematurity) between ranibizumab and laser therapy. The same study also reported similar scores for the different groups in an assessment using a scale of early learning but did not statistically compare the groups.
  - No evidence relating to quality of life was identified for ranibizumab compared to bevacizumab.

- **Retreatment[6] (important outcome).**
  - *For ranibizumab vs laser therapy:* One RCT and RCT extension study provided very low certainty evidence of retreatment for a single patient (1.9%) after 0.1mg ranibizumab and 5% of patients after laser therapy. There were no retreatments after 0.2mg ranibizumab up to approximately two years follow-up. The groups were not statistically compared. A retrospective cohort study provided very low certainty evidence that 20% of eyes that initially received laser therapy had retreatment up to six months after initial treatment. It was not clear if any patients from the ranibizumab group had received retreatment in this study.
  - No evidence relating to retreatment was identified for ranibizumab compared to bevacizumab.

- **Development of infection (important outcome).**

[5] Treatment failure is defined as retreatment within 24 weeks for ranibizumab or within 4 weeks for laser therapy

[6] Retreatment is defined as further treatment post 24 weeks for ranibizumab or post 4 weeks for laser therapy

- *For ranibizumab vs laser therapy:* One RCT provided very low certainty evidence of a single case of endophthalmitis (1.3%) at 24 weeks follow-up after 0.1mg ranibizumab. There were no cases of endophthalmitis after 0.2mg ranibizumab or after laser therapy. The groups were not statistically compared. There were no cases of endophthalmitis in a second RCT comparing ranibizumab and laser therapy up to approximately 12 months follow-up.
- *For ranibizumab, laser therapy and bevacizumab:* There were no cases of endophthalmitis in a retrospective cohort study comparing ranibizumab, laser therapy and bevacizumab at 18-20 months follow-up.

In terms of safety:

- **Adverse effects.**
  - *For ranibizumab vs laser therapy:* One RCT provided low certainty evidence of serious ocular adverse events in 1% of patients after 0.1mg ranibizumab and 6% after 0.2mg ranibizumab or laser therapy after 24 weeks follow-up. Serious non-ocular adverse events occurred in 32% to 33% of patients for all three groups. Rates of any ocular adverse event were 41% after 0.1mg ranibizumab and 30% and 34% after 0.2mg ranibizumab or laser therapy respectively. Rates of any non-ocular adverse event were 85% for 0.2mg ranibizumab, 82% for 0.1mg ranibizumab and 77% for laser therapy. The groups were not statistically compared. This RCT also reported plasma VEGF up to 29 days follow-up for two ranibizumab doses and laser therapy. In all three groups, levels reduced from day 1 to day 15 and then increased to day 29. The groups were not statistically compared. For the ranibizumab groups, serum ranibizumab levels reduced from day 1 to day 15 and then further reduced to day 29 (to approximately 1,000 pg/mL in both groups). An extension study to this RCT provided very low certainty evidence of no serious non-ocular adverse events related to the study intervention at last follow-up when patients were approximately two years old (low certainty). A second RCT provided low certainty evidence of no cases of specified ocular adverse events with ranibizumab or laser therapy up to approximately 12 months follow-up. One retrospective cohort study provided very low certainty evidence of no statistically significant difference between ranibizumab and laser therapy for specified major complications up to approximately three years follow-up, with no deaths, major systemic complications or adverse neurodevelopmental outcomes at last follow-up.
  - *For ranibizumab, laser therapy and bevacizumab:* One retrospective cohort study provided very low certainty evidence of no major ocular complications with ranibizumab, laser therapy or bevacizumab at 18-20 months follow-up.
  - *For ranibizumab vs bevacizumab:* One retrospective cohort study provided very low certainty evidence of no statistically significant differences between ranibizumab and bevacizumab for specified major complications at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab, with no deaths, major systemic complications or glaucoma cases at last follow-up.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- One retrospective cohort study reported high myopia in statistically significantly fewer patients with Zone I ROP after ranibizumab or bevacizumab compared to laser therapy.

There was no statistically significant difference between treatment groups for patients with Zone II ROP. A post-hoc analysis from an RCT reported lower cases of treatment failure for patients who received ranibizumab and had Zone I or Zone II ROP than for patients with aggressive posterior ROP. For patients who received laser therapy, treatment failure cases were lower for Zone II ROP but appeared similar for Zone I and aggressive posterior ROP. However, neither the treatment groups nor disease groups were statistically compared. In a retrospective cohort study, significant independent risk factors for treatment failure included Zone I ROP, early postmenstrual age at initial treatment, low Apgar score, pneumonia and multiple births. In two retrospective cohort studies, an initial ROP stage of 3 was associated with a statistically significant higher incidence of major complications than an initial ROP stage of 2.

Criteria used to define preterm infants eligible to receive first line drug treatment with ranibizumab:

- The RAINBOW RCT included preterm infants (birth weight <1,500g) with bilateral ROP Zone I stage 1+, 2+ 3 or 3+ or Zone II stage 3+ or aggressive posterior ROP[7]. This RCT excluded infants with ROP in Zone II, stage 2+; ocular and neurological comorbidities that might result in confounding visual impairment and active ocular infection within five days before investigational treatment.
- The RCT by Zhang et al (2017) screened preterm infants (birth weight <2,000g or birth weight ≥2,000g but with severe systemic disorders) for ROP. Infants with binocular Zone II treatment-requiring ROP (i.e. ROP with Stage 2+ or 3+ in Zone II) were eligible for inclusion. This RCT excluded preterm infants with ROP in Zone I, Stage 4 or Stage 5 ROP and aggressive posterior ROP in either eye.
- The retrospective cohort study by Chmielarz-Czarnocińska et al (2021) screened preterm infants (gestational age ≤33 weeks and birth weight <1,800g or high risk as determined by a neonatologist) for ROP. Treatment criteria were based on the ETROP[8] study with some cases also receiving treatment after the acute-phase treatment criteria defined by ETROP at the discretion of the examining ophthalmologist. The authors stated that treatment was determined by the treating ophthalmologist depending on the severity of the disease with ranibizumab preferred for infants with Zone I ROP with plus disease, Zone I ROP stage 3 without plus disease and for aggressive posterior ROP.
- The retrospective cohort study by Gunay et al (2017) stated that decisions to treat infants were made according to the indications established in the ETROP study[8]. This study excluded infants with stage 4 or 5 ROP and infants who received supplemental treatment with intravitreal injections following failed laser therapy.
- The retrospective cohort studies by Kang et al (2019) and Kang et al (2018) both screened preterm infants (gestational age <32 weeks and birth weight <1,500g or unstable clinical course as determined by the primary neonatologist) for ROP. Infants meeting the treatment criteria had type 1 ROP as defined in the ETROP study[9] with some cases receiving earlier treatment at the discretion of the primary ophthalmologist.

[7] In ROP, the three zones refer to specific locations of the eye centred around the optic nerve. Zone I is the innermost area and Zone III the outermost. There are five stages of ROP which relate to the severity of the condition from Stage 1 (mild) to Stage 5 (total retinal detachment). Retinopathy of prematurity - RNIB - See differently. Severe ROP is associated with dilation and tortuosity of the retinal vessels, termed plus disease (International Classification of Retinopathy of Prematurity, Third Edition - Ophthalmology (aaojournal.org))

[8] Early Treatment for Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch. Ophthalmol. 2003;121, 1684–1694

[9] Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-48

Kang et al (2018) stated that there was a gradual change in preference from bevacizumab to ranibizumab over the study period.
- In the retrospective cohort study by Ling et al (2020) indications for treatment were infants whose retinopathy met the criteria of Type I ROP in the BEAT-ROP study[10].

Please see the results table (section 5) in the review for further details of outcomes.

Limitations:

Limitations reducing certainty in the RAINBOW RCT outcomes included uncertainty about differences between the groups at baseline and in the way the two groups were treated, incomplete follow-up and uncertainty about whether 'unfavourable structural retinal outcomes' were measured in a reliable way. Limitations reducing certainty in a second RCT included differences in the way the two groups were treated. Limitations reducing certainty in the retrospective cohort studies included lack of clarity about the similarity between the groups at baseline for all but one of the five studies, lack of adjustment for potential confounding factors and uncertainty about whether follow-up was complete. For all studies, additional uncertainty for some outcomes included lack of statistical analysis, lack of blinding for subjective outcomes and imprecision because no events occurred for some outcomes.

Conclusion:

This evidence review includes two RCTs, one RCT extension study and five retrospective cohort studies.

There was data from RCTs and an RCT extension study on the number of cases of outcomes with ranibizumab or laser therapy for the critical outcomes of unfavourable structural retinal outcomes and sight impairment/ severe sight impairment. These generally reported lower numbers of these unfavourable outcomes with ranibizumab, particularly at a dose of 0.2mg when different doses were used in the RCT. However, they did not provide any statistical analysis comparing the treatment groups. Statistical comparison of treatment groups for the critical outcomes of unfavourable structural retinal outcomes, high myopia and sight impairment/ severe sight impairment was available from an RCT extension study and/ or retrospective cohort studies. For these critical outcomes, the statistical analyses either reported no statistically significant difference between ranibizumab and laser therapy or bevacizumab or reported results that favoured ranibizumab.

There was data from RCTs, without statistical comparison of the treatment groups, on the number of cases for the important outcome of treatment failure. Both RCTs reported a higher number of cases of treatment failure with ranibizumab than laser therapy. In three retrospective cohort studies that conducted statistical comparison of treatment groups, there was no statistically significant difference in treatment failure between ranibizumab, laser therapy and bevacizumab. However, there was some evidence of statistically significantly more cases of treatment failure for ranibizumab compared to bevacizumab in two studies. Limited evidence was identified for retreatment, with no comparison of treatment groups for this important outcome. For the important outcome of quality of life, one RCT extension study reported no statistically significant difference between ranibizumab and laser therapy. For the important outcome of development of infection, only one case was reported across the three studies that reported this outcome, suggesting that this outcome rarely occurs with ranibizumab, laser therapy or bevacizumab.

[10] The reference for the BEAT-ROP study given by the study authors is the same as the reference for the ETROP study provided by Chmielarz-Czarnocińska et al (2021) and Gunay et al 2017

For safety outcomes, numbers of serious ocular and non-ocular adverse events appeared to be similar with ranibizumab and laser therapy within one RCT, but the groups were not statistically compared. Two retrospective cohort studies that conducted statistical comparison of treatment groups reported no statistically significant difference in major complications between ranibizumab and laser therapy or bevacizumab.

The studies identified for this review therefore provide moderate to very low certainty evidence that overall, for preterm infants with ROP there may be little difference in effectiveness and safety for ranibizumab and laser therapy or bevacizumab. Where studies did report a statistical advantage for one treatment, this favoured ranibizumab for unfavourable structural retinal outcomes, high myopia and sight impairment/ severe sight impairment, but not for treatment failure.

There was limited evidence that patients with Zone I ROP might benefit from ranibizumab or bevacizumab more than laser therapy in terms of high myopia and, in a post-hoc analysis from an RCT, there appeared to be lower cases of treatment failure for patients who received ranibizumab and had Zone I or Zone II ROP rather than aggressive posterior ROP based on a descriptive report of number of cases. However, Zone I ROP was a significant risk factor for treatment failure, compared to Zone II ROP, in a retrospective cohort study along with early postmenstrual age at initial treatment, low Apgar score, pneumonia and multiple births. An initial ROP stage of 3 was associated with a higher incidence of major complications than an initial ROP stage of 2 in two retrospective cohort studies.

There was no evidence on cost effectiveness.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In preterm infants, what is the clinical effectiveness of ranibizumab as first line drug treatment compared with standard of care for ROP?

2. In preterm infants, what is the safety of ranibizumab as first line drug treatment compared with standard of care for ROP?

3. In preterm infants, what is the cost effectiveness of ranibizumab as first line drug treatment compared with standard of care for ROP?

4. From the evidence selected, are there any subgroups of preterm infants that may benefit more from ranibizumab as first line drug treatment than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define those preterm infants diagnosed with ROP who are eligible to receive first line drug treatment with ranibizumab?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 18th March 2022.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Seven studies (published in nine papers) were identified for inclusion. Two RCTs compared ranibizumab and laser therapy in preterm infants with ROP. These were the RAINBOW RCT (published in Fleck et al 2022, Marlow et al 2021, Stahl et al 2019) and a RCT by Zhang et al (2017). Two retrospective cohort studies compared ranibizumab and laser therapy (Chmielarz-Czarnocińska et al 2021, Kang et al 2019) in preterm infants with ROP. Two retrospective cohort studies compared ranibizumab, laser therapy and bevacizumab (Gunay et al 2017, Ling et al 2020) in preterm infants in ROP. One retrospective cohort study compared ranibizumab and bevacizumab (Kang et al 2018) in preterm infants with ROP. No studies were identified comparing ranibizumab and cryotherapy or argon laser.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

No cost effectiveness studies were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Chmielarz-Czarnocińska et al 2021 Retrospective cohort study 1 centre, Poland	176 preterm infants with ROP (350 eyes) Ranibizumab: n=61 (120 eyes) Laser therapy: n=115 (226 eyes) Zone I ROP: 11.3% Zone II ROP: 78.2% AP ROP: 10.4% No comparison of baseline characteristics for treatment groups. Authors stated that treatment was determined by the treating ophthalmologist depending on severity of disease with ranibizumab preferred for infants with Zone I ROP with plus disease, Zone I ROP stage 3 without plus disease and for AP ROP No subgroups reported	**Intervention** Ranibizumab 0.25mg/ 0.025mL **Comparison** Laser therapy No details of any concomitant treatments reported	Follow-up up to 6 months. Mean follow-up not reported **Important outcomes** • Treatment failure[a] • Retreatment
Gunay et al 2017 Retrospective cohort study 2 centres, Turkey	134 preterm infants with ROP (264 eyes) Ranibizumab: n=22 Laser therapy: n=55 Bevacizumab: n=57 Number of eyes in each group not reported Zone I ROP: 13.3% Zone II ROP: 68.7% AP ROP: 18.7% The groups were similar in terms of gestational age	**Intervention** Ranibizumab 0.25mg/ 0.025mL **Comparison** Laser therapy Bevacizumab 0.625mg/ 0.025mL Patients receiving ranibizumab or bevacizumab received topical antibiotics for 1 week after treatment	Mean ± SD follow-up (months): • Ranibizumab: 18.96 ± 4.79 • Laser therapy: 20.68 ± 6.89 • Bevacizumab: 19.40 ± 6.43 p=0.602 **Critical outcomes** • Unfavourable structural retinal outcomes • High myopia

Study	Population	Intervention and comparison	Outcomes reported
	and birth weight. There was a statistically significant difference in PMA at treatment (p=0.001) and there was a statistically significantly higher percentage of patients with Zone II ROP in the laser therapy group (p=0.001) High myopia reported by ROP disease stage	Patients receiving laser therapy received steroid-antibiotic drops for 1 week after treatment	**Important outcomes** • Treatment failure • Development of infection • Safety
Kang et al 2019 Retrospective cohort study 1 centre, South Korea	165 preterm infants with ROP (314 eyes) Ranibizumab: 153 eyes Bevacizumab: 161 eyes Number of patients in each group not reported Zone I ROP: 16.2% Zone II ROP: 72.3% Zone III ROP: 11.5% Stage 2 ROP: 10.2% Stage 3 ROP: 89.8% AP ROP: 7.2% Presence of + disease: 66.6% The groups were similar for sex, body weight and gestational age. PMA at primary treatment was higher for the laser therapy group (p=0.012). There were statistically significantly more Zone I (22% vs 11%, p=0.006) and AP ROP cases (7% vs 0%, p<0.001) in the ranibizumab group Safety outcomes analysed by disease stage and patient characteristics	**Intervention** Ranibizumab 0.25mg/ 0.025mL **Comparison** Laser therapy No details of any concomitant treatments reported	Mean ± SD follow-up (months): 36.3 ± 31.9 **Critical outcomes** • Unfavourable structural retinal outcomes • Sight impairment/ severe sight impairment **Important outcomes** • Treatment failure • Safety • Major complications
Kang et al 2018 Retrospective cohort study 2 centres, South Korea	83 preterm infants with ROP (153 eyes) Ranibizumab: 52 eyes Bevacizumab: 101 eyes Number of patients in each group not reported Zone I ROP: 22.2% Zone II ROP: 69.9% Zone III ROP: 7.8% AP ROP: 7.2% Mean gestational age was statistically significantly higher for ranibizumab vs	**Intervention** Ranibizumab 0.2mg/ 0.02mL **Comparison** Bevacizumab 0.625mg/ 0.025mL No details of any concomitant treatments reported	Mean ± SD follow-up (months): • Ranibizumab: 13.9 ± 12.5 • Bevacizumab: 30.9 ± 18.4 p<0.001 **Critical outcomes** • Unfavourable structural retinal outcomes • Sight impairment/ severe sight impairment **Important outcomes**

Study	Population	Intervention and comparison	Outcomes reported
	bevacizumab, p=0.013. Mean body weight was statistically significantly higher for ranibizumab (p<0.001) There was a higher proportion of eyes with Zone I ROP (p<0.001) and stage 2 ROP (p=0.022) for ranibizumab. There was a higher proportion of eyes with Zone II ROP (p=0.009) and stage 3 ROP (p=0.022) for bevacizumab Incidence of major complications analysed by ROP disease stage and patient characteristics		• Treatment failure[b] • Safety • Major complications
Ling et al 2020 Retrospective cohort study 1 centre, Taiwan	176 preterm infants with ROP (340 eyes) Ranibizumab: n=25 (48 eyes) Laser therapy: n=33 (61 eyes) Bevacizumab: n=118 (231 eyes) Zone I ROP: 11.1% Zone II ROP: 88.9% Groups were similar for all baseline demographic and ROP characteristics Treatment failure analysed by ROP disease stage	**Intervention** Ranibizumab 0.25mg/ 0.025mL **Comparison** Laser therapy Bevacizumab 0.625mg/ 0.025mL No details of any concomitant treatments reported	Mean ± SD follow-up 197.3 ± 110 weeks **Critical outcomes** • Unfavourable structural retinal outcomes **Important outcomes** • Treatment failure
RAINBOW (reported in Fleck et al 2022, Marlow et al 2021 and Stahl et al 2019) RCT and two-year interim analysis from extension study Multi-centre (87 centres), 26 countries (Japan (16 centres; 29 patients), US (12;21), India (6;29), Turkey (6;14), Russia	225 preterm infants with ROP (448 eyes) Ranibizumab 0.2mg: n=74 (148 eyes) Ranibizumab 0.1mg: n=77 (152 eyes) Laser therapy: n=74 (148 eyes) Extension study analysis n=153 Zone I ROP: 38.2% Zone II ROP: 61.3% AP ROP: 13.3% No statistical comparison of baseline characteristics. Authors reported that gestational age was slightly lower in the	**Intervention** Group 1: Ranibizumab 0.2mg Group 2: Ranibizumab 0.1mg Up to 2 additional treatments with ranibizumab allowed in each eye at a minimum of 28-day intervals **Comparison** Laser therapy Supplementary laser treatment for skip lesions allowed up to day 11	RCT 24 weeks follow-up. Extension study analysis at age 20-28 months (with age corrected for prematurity) **Critical outcomes** • Unfavourable structural retinal outcomes (up to 2 years follow-up) • High myopia at age 20-28 months • Sight impairment/ severe sight impairment (up to 2 years follow-up) **Important outcomes** • Treatment failure (up to 24 weeks follow-up[a]) • Quality of life at age 20-28 months assessed using the Children's

Study	Population	Intervention and comparison	Outcomes reported

(5;20), Italy (4;14), Austria (3;6), Czech Republic (3;9), Greece (3;10), Romania (3;16), UK (3;5), Belgium (2;10), Croatia (2;9), France (2;3), Germany (2;3), Hungary (2;2), Malaysia (2;2), Poland (2;3), Taiwan (2;7), Denmark (1;1), Egypt (1;3), Estonia (1;2), Lithuania (1;1), Mexico (1;6), Saudi Arabia (1;1), Slovakia (1;1))	ranibizumab 0.2mg group than the other groups. The figures also suggest that mean birth weight was lower in the ranibizumab 0.2mg group
	
	Authors stated that 'most other baseline characteristics were well balanced between study groups"
	
	Categorisation of ROP described as 'similarly distributed across treatment groups at baseline"
	
	Treatment failure outcomes reported by ROP disease stage
		No details of any concomitant treatments reported	Visual Function Questionnaire[c] and the Mullen Scales of Early Learning[d]
			• Retreatment[a] (up to 2 years follow-up)
			• Development of infection (up to 2 years follow-up)
			• Safety (up to 2 years follow-up)
			  • Deaths
			  • Serious ocular adverse events
			  • Ocular adverse events
			  • Non-ocular serious adverse events
			  • Non-ocular adverse events
			  • Serum plasma VEGF

Zhang et al 2017 RCT Single-centre, China	50 preterm infants with Zone II ROP (100 eyes) Ranibizumab: n=25 (50 eyes) Laser therapy: n=25 (50 eyes) Groups were similar at baseline for gestational age, birth weight, sex ratio, proportion of single or twin births and delivery methods No subgroups reported	**Intervention** Ranibizumab 0.3mg in 0.03mL An ophthalmic antibiotic eye drop was prescribed for the treated eye to begin immediately and continued 4 times a day for 7 days **Comparison** Laser therapy Topical steroid and cycloplegicmydriatic were administered for 1 week after laser therapy Eyes with ROP recurrence had crossover treatment	Mean ± SD follow-up (weeks) for all outcomes: • Ranibizumab: 49.94 ± 14.67 • Laser therapy: 54.03 ± 12.40 p=0.37 **Critical outcomes** • Unfavourable structural retinal outcomes **Important outcomes** • Treatment failure • Development of infection • Safety

Abbreviations
AP: Aggressive posterior; mg: Milligrams; mL: Millilitres; PMA: Postmenstrual age; RCT: Randomised controlled trial; ROP: Retinopathy of prematurity; SD: Standard deviation; VEGF: Vascular endothelial growth factor

a Treatment failure was defined as retreatment within 24 weeks for ranibizumab and within 4 weeks for laser therapy in the PICO document. Retreatment was defined as retreatment post 24 weeks for ranibizumab and post 4 weeks for laser therapy in the PICO document
b No timeframe was provided for retreatment in this study. These results are presented as treatment failure due to the absence of any evidence to confirm that retreatment was required after 24 weeks
c The Children's Visual Function Questionnaire for children under 3 years of age is a validated questionnaire with 4 vision-related subscales (competence, personality, family impact and treatment effect), 2 subscales for general health and general vision and a summative composite score. Subscale and summary scores are standardised to range from 0 to 100 with higher scores indicating better function/ quality of life
d The Mullen Scales of Early Learning assess developmental progress with 3 subscales (visual recognition, receptive language and expressive language). The mean population norm T-score is 50 (SD 10)

5. Results

In preterm infants, what is the clinical effectiveness and safety of ranibizumab as first line drug treatment compared with standard of care for ROP?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Unfavourable structural retinal outcomes **Certainty of evidence:** Low to very low	Unfavourable structural retinal outcomes include substantial temporal retinal vessel dragging causing structural features of macular ectopia; or retrolental membrane obscuring the posterior pole, posterior retinal fold, or retinal detachment involving the macula. This outcome is important for patients because they can all contribute to poor vision or blindness. In total, two RCTs, one extension study from the RAINBOW RCT and four retrospective cohort studies provided evidence relating to unfavourable structural retinal outcomes in infants with ROP for between 24 weeks and approximately three years follow-up. Results comparing ranibizumab and laser therapy were available from the two RCTs, the RCT extension study and one retrospective cohort study. Results comparing ranibizumab, laser therapy and bevacizumab were available from two retrospective cohort studies. Results comparing ranibizumab and bevacizumab were available from one retrospective cohort study. **At ≥3 years:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Kang et al 2019) reported *statistically significantly fewer* cases of retinal detachment and temporal macular dragging for ranibizumab vs laser therapy at mean ± SD 36.3 ± 31.9 months follow-up. Retinal detachment occurred in 1/53 eyes (0.7%) after ranibizumab and 8/161 eyes (5.0%) after laser therapy (p=0.037). Temporal macular dragging occurred in 1/53 eyes (0.7%) after ranibizumab and 7/161 eyes (4.3%) after laser therapy (p=0.039). (**VERY LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Ling et al 2019) reported *no statistically significant difference* in progression to retinal detachment between ranibizumab (1/48 eyes, 2.1%), laser therapy (3/61 eyes, 4.9%) and bevacizumab (2/231 eyes, 0.9%) (p=0.2701) at mean ± SD 197.3 ± 110 weeks follow-up. (**VERY LOW)** **At 18 months to 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported *no statistically significant difference* in structural abnormalities[11] present at age 20-28 months (corrected for prematurity) between two ranibizumab doses (0.2mg 1/56, 1.8%; 0.1mg 1/51, 2.0%) and laser therapy (4/44, 9.1%). The odds ratio of having no structural abnormality was 5.68 (95%CI 0.60 to 54), p=0.10 for ranibizumab 0.2mg vs laser therapy and 4.82 (95%CI 0.52 to 45), p=0.14 for ranibizumab 0.1mg vs laser therapy. **(LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported no unfavourable anatomical outcomes[12] for 22 patients with ranibizumab or 55 patients with bevacizumab and one unfavourable anatomical outcome (retinal detachment) in one of 57 patients (1.8%) with laser therapy. Mean follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months

[11] In the RAINBOW RCT structural abnormalities included abnormalities that have potential effects on visual acuity: retrolental membrane obscuring the view of the posterior pole, substantial temporal retinal vessel dragging causing abnormal structural features or macular ectopia, posterior retinal fold involving the macula, or retinal detachment involving the macula

[12] Unfavourable anatomical outcomes were any of: dragging of the disc, localised tractional or non-tractional membranes at posterior pole or in the retinal periphery and total or partial retinal detachment

Outcome	Evidence statement
	for laser therapy and 19.40 ± 6.43 months for bevacizumab. No statistical comparison between groups reported. **(VERY LOW)** **At approximately 1 year:** *Ranibizumab vs laser therapy* • One RCT (Zhang et al 2017) reported no retinal detachment cases in patients who received ranibizumab (n=25) or laser therapy (n=25). Mean ± SD follow-up was 49.94 ± 14.67 weeks for ranibizumab and 54.03 ± 12.40 weeks for laser therapy. **(LOW)** *Ranibizumab vs bevacizumab* • One retrospective cohort study (Kang et al 2018) reported *no statistically significant difference* in cases of retinal detachment or temporal macular dragging between ranibizumab and bevacizumab at mean ± SD follow-up of 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab. Retinal detachment occurred in 0/52 eyes (0%) after ranibizumab and 1/101 eyes (1.0%) after bevacizumab (p=0.660). Temporal macular dragging occurred in 1/52 eyes (1.9%) after ranibizumab and 0/101 eyes (0%) after bevacizumab (p=0.340)[13]. (**VERY LOW)** **At 24 weeks:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported number of unfavourable structural retinal outcomes at 24 weeks follow-up for two ranibizumab doses (0.2mg 1/74, 1.4%; 0.1mg 5/77, 6.5%) and laser therapy (7/74, 9.5%). No statistical comparison between groups reported. **(LOW)** **For ranibizumab vs laser therapy: One RCT provided low certainty evidence of unfavourable structural retinal outcomes in 1% and 7% of patients who received 0.2mg and 0.1mg of ranibizumab respectively and 10% of patients who received laser therapy after 24 weeks follow-up. The groups were not statistically compared. An extension study to this RCT provided low certainty evidence of no statistically significant difference in structural abnormalities between ranibizumab and laser therapy at age 20-28 months (corrected for prematurity). A second RCT reported no cases of retinal detachment with either ranibizumab or laser therapy at approximately 12 months follow-up. One retrospective cohort study provided very low certainty evidence of statistically significantly fewer cases of retinal detachment and temporal dragging for ranibizumab compared to laser therapy at a mean of 36 months follow-up.** **For ranibizumab, laser therapy and bevacizumab: One retrospective cohort study provided very low certainty evidence of no statistically significant difference in retinal detachment between ranibizumab, laser therapy and bevacizumab at a mean of 197 weeks follow-up. A second retrospective study provided very low certainty evidence of a single unfavourable anatomical outcome (1.8%) in a patient who received laser therapy and no cases with ranibizumab or bevacizumab at 18-20 months follow-up. The groups were not statistically compared.** **For ranibizumab vs bevacizumab: One retrospective cohort study provided very low certainty evidence of no statistically significant difference in retinal detachment or temporal macular dragging between ranibizumab and bevacizumab at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab.**
High myopia **Certainty of evidence:** Low to very low	High myopia (for example, <5 Dioptres), is important for patients because this contributes to patients being dependent on glasses. Glasses are essential to wear during the child's "critical period" of development up to 7 years. It can be difficult for many patients to wear glasses earlier than this age and non-compliance with not wearing them can lead to a "lazy eye" (amblyopia).

[13] There is a discrepancy in the paper about whether the one patient with temporal macular dragging received bevacizumab or ranibizumab. The result from the data table (rather than the text) is reported here

Outcome	Evidence statement
	In total, one extension study from the RAINBOW RCT and one retrospective cohort study provided evidence relating to high myopia outcomes in infants with ROP at 18 months to two years follow-up. Results comparing ranibizumab and laser therapy were available from the RCT extension study. Results comparing ranibizumab, laser therapy and bevacizumab were available from the retrospective cohort study. **At 18 months to 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported *statistically significantly fewer* cases of high myopia present in at least one eye at age 20-28 months (corrected for prematurity) for 0.2mg ranibizumab (4/55, 7.3%) vs laser therapy (14/41, 34.1%) (OR 0.15 (95%CI 0.05 to 0.50) p=0.0021)[14]. The prevalence of high myopia per eye at age 20-28 months was also *statistically significantly lower* for 0.2mg ranibizumab (5/110 eyes, 4.5%) vs laser therapy (16/82 eyes, 19.5%) (OR 0.19 (95%CI 0.05 to 0.69) p=0.012). There was *no statistically significant difference* in the prevalence of high myopia per eye at age 20-28 months between 0.1mg ranibizumab (8/98 eyes, 8.2%) and laser therapy (16/82 eyes, 19.5%) (OR 0.44 (95%CI 0.14 to 1.32) p=0.14). **(LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported *no statistically significant difference* in the proportion of patients with high myopia between ranibizumab (13.6%), laser therapy (14%) and bevacizumab (12.7%) (p=0.979). Mean follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. **(VERY LOW)** **For ranibizumab vs laser therapy: One RCT extension study provided low certainty evidence of statistically significantly less high myopia for 0.2mg ranibizumab compared to laser therapy at age 20-28 months (corrected for prematurity). There was no statistically significant difference in high myopia for 0.1mg ranibizumab compared to laser therapy in this study.** **For ranibizumab, laser therapy and bevacizumab: One retrospective cohort study provided very low certainty evidence of no statistically significant difference in high myopia between ranibizumab, laser therapy and bevacizumab at approximately 18-20 months follow-up.**
Sight impairment/ severe sight impairment **Certainty of evidence:** Low to very low	Sight impairment/ severe sight impairment includes irreversible sight impairment outcomes such as amblyopia which cannot be treated. High myopia which does not lead to amblyopia would not overlap as it is treatable with glasses. This outcome is important for patients because this is a disability and may restrict many activities and occupations for the patient later in life. In total, one RCT (RAINBOW), one extension study from the RAINBOW RCT and two retrospective cohort studies provided evidence relating to sight impairment/ severe sight impairment in infants with ROP for between 24 weeks and approximately three years follow-up. Results comparing ranibizumab and laser therapy were available from the RCT, the RCT extension study and one retrospective cohort study. Results comparing ranibizumab and bevacizumab were available from one retrospective cohort study. Outcomes relating to sight impairment reported by the studies included cases of nystagmus[15], strabismus[16],

[14] Outcome not reported for ranibizumab 0.1mg

[15] Nystagmus is a rhythmical, repetitive and involuntary movement of the eyes which the patient has no control over. There is no cure for nystagmus and sight problems are common (Nystagmus | Great Ormond Street Hospital (gosh.nhs.uk)). However, it is also possible to have this condition with normal or near normal vision

[16] Strabismus is a squint, where the eyes point in different directions. If untreated in young children, lazy eye (amblyopia) can develop with poor vision in the eye with the squint (Squint (strabismus) - Moorfields Eye Hospital). However, it is also possible to have this condition with normal or near normal vision

Outcome	Evidence statement
	abnormal fixation and abnormal pupil reaction (not further defined in the studies but may be associated with sight impairment/ severe sight impairment). **At 3 years:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Kang et al 2019) reported *no statistically significant difference* in strabismus operations between ranibizumab (21/153 eyes, 13.7%) and laser therapy (26/161 eyes, 16.1%) (p=0.636) at mean ± SD 36.3 ± 31.9 months follow-up. (**VERY LOW)** **At 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported number of nystagmus cases, strabismus cases, abnormal fixation cases and abnormal pupil reaction cases at age 20-28 months (corrected for prematurity) for two ranibizumab doses and laser therapy. Nystagmus occurred in 2/55 patients (3.6%) after 0.2mg ranibizumab, 3/50 (6.0%) after 0.1mg ranibizumab and 5/41 (12.2%) after laser therapy. Strabismus occurred in 11/55 patients (20.0%) after 0.2mg ranibizumab, 12/49 (24.5%) after 0.1mg ranibizumab and 13/41 (31.7%) after laser therapy. Abnormal fixation occurred in 1/55 patients (1.8%) after 0.2mg ranibizumab, 8/52 (15.4%) after 0.1mg ranibizumab and 2/44 (14.5%) after laser therapy. Abnormal pupil reaction occurred in 0/55 patients (0%) after 0.2mg ranibizumab, 3/52 (6.0%) after 0.1mg ranibizumab and 1/42 (2.4%) after laser therapy. No statistical comparison between groups reported. **(LOW)** **At approximately 1 year[17]:** *Ranibizumab vs bevacizumab* • One retrospective cohort study (Kang et al 2018) reported *statistically significantly fewer* strabismus operations for ranibizumab (0/52 eyes, 0%) vs bevacizumab (21/101 eyes, 20.8%) (p<0.001) at mean ± SD follow-up of 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab. (**VERY LOW)** **At 24 weeks:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported number of nystagmus cases at 24 weeks follow-up for two ranibizumab doses (0.2mg 1/73, 1.4%; 0.1mg 0/76, 0%) and laser therapy (0/69, 0%). No statistical comparison between groups reported. **(LOW)** **For ranibizumab vs laser therapy: One RCT provided low certainty evidence of a single nystagmus case (1.4%) at 24 weeks follow-up for 0.2mg ranibizumab. There were no cases of nystagmus after 0.1mg ranibizumab or laser therapy. An extension study to this RCT provided low certainty evidence of outcomes at age 20-28 months (corrected for prematurity). This reported nystagmus in 3.6% and 6.0% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 12.2% after laser therapy. This study also reported strabismus in 20.0% and 24.5% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 31.7% after laser therapy. Abnormal fixation occurred in 1.8% and 15.4% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 14.5% after laser therapy. Abnormal pupil reaction occurred in 0% and 6.0% of patients after 0.2mg and 0.1mg of ranibizumab respectively and 2.4% after laser therapy. This RCT and RCT extension study did not statistically compare the groups. One retrospective cohort study provided very low certainty evidence of no statistically significant difference in strabismus operations between ranibizumab and laser therapy at a mean of 36 months follow-up.**

[17] Based on the mean follow-up for the ranibizumab group

Outcome	Evidence statement
	For ranibizumab vs bevacizumab: One retrospective cohort study provided very low certainty evidence of statistically significantly fewer strabismus operations for ranibizumab compared to bevacizumab at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab.
Important outcomes	
Treatment failure **Certainty of evidence:** Moderate to very low	Treatment failure (for example, retreatment within 24 weeks for ranibizumab or within 4 weeks for diode laser) is important for patients because they may need to come back for more treatment which can be inconvenient for the patient or put them at risk if anaesthesia is needed for the treatment. In total, two RCTs and five retrospective cohort studies provided evidence relating to treatment failure in infants with ROP for between 24 weeks and approximately three years follow-up. Results comparing ranibizumab and laser therapy were available from two RCTs and two retrospective cohort studies. Results comparing ranibizumab, laser therapy and bevacizumab were available from two cohort studies. Results comparing ranibizumab and bevacizumab were available from one retrospective cohort study. **At ≥3 years:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Kang et al 2019) reported *no statistically significant difference* in treatment failure between ranibizumab (15/153 eyes, 9.8%) and laser therapy (22/161 eyes, 13.7%) (p=0.196) at mean ± SD 36.3 ± 31.9 months follow-up. Mean time to retreatment was 5.7 weeks for ranibizumab and 2.3 weeks for laser therapy. (**VERY LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Ling et al 2019) reported *no statistically significant difference* in treatment failure between ranibizumab (10/48 eyes, 20.8%), laser therapy (11/61 eyes, 18.0%) and bevacizumab (23/231 eyes, 10.0%) (p=0.0528) at mean ± SD 197.3 ± 110 weeks follow-up. In multivariable regression analysis, ranibizumab was a *statistically significant* independent risk factor for treatment failure compared to bevacizumab (OR 2.922 (95%CI 1.179 to 7.240), p=0.0205). Mean ± SD time to retreatment was 8.3 ± 1.6 weeks for ranibizumab, 3.6 ± 1.4[18] weeks for laser therapy and 8.8 ± 3.9 weeks for bevacizumab. (**VERY LOW)** **At approximately 18 months:** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported *no statistically significant difference* in treatment failure between ranibizumab (3/22, 13.6%), laser therapy (0/57, 0%) and bevacizumab (3/55, 5.5%) (p=0.098) at mean ± SD follow-up of 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. Mean ± SD time to retreatment was 8.7 ± 1.5 weeks for ranibizumab and 14 ± 2.65 weeks for bevacizumab. **(VERY LOW)** **At approximately 1 year:** *Ranibizumab vs laser therapy* • One RCT (Zhang et al 2017) reported treatment failure in 11/25 (44.0%) patients who received ranibizumab and 1/25 (4.0%) patients who received laser therapy at mean ± SD follow-up of 49.94 ± 14.67 weeks for ranibizumab and 54.03 ± 12.40 weeks for laser therapy. No statistical comparison between groups reported. Time to treatment failure ranged from 4 to 13 weeks for ranibizumab and was one week for laser therapy. **(MODERATE)** *Ranibizumab vs bevacizumab* • One retrospective cohort study (Kang et al 2018) reported that *statistically significantly more* eyes required additional anti-VEGF treatment for ranibizumab (7/52 eyes, 13.5%) vs bevacizumab (4/101 eyes, 4.0%)

[18] The mean ± SD time to recurrence for laser therapy suggests some infants received retreatment post 4 weeks but this number is not reported

Outcome	Evidence statement
	(p=0.037). The number of eyes requiring any additional treatment was 7/52 eyes (13.5%) for ranibizumab and 8/101 eyes (7.9%) for bevacizumab. No statistical comparison between groups reported. Mean ± SD follow-up was 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab. Time to retreatment not reported[19]. **(VERY LOW)** **At approximately 6 months:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported treatment failure up to 24 weeks follow-up for two ranibizumab doses (0.2mg 23/74, 31.1%; 0.1mg 24/77, 31.2%) and laser therapy (10/74, 13.5%). No statistical comparison between groups reported. Additional treatments after ranibizumab occurred between days 1 and 169 after initial treatment. Additional treatments after laser therapy occurred between days 1 and 29. **(LOW)** • One retrospective cohort study (Chmielarz-Czarnocińska et al 2021) reported treatment failure in 80/120 eyes (66.7%) with ranibizumab and 0/226 eyes with laser therapy at up to six months follow-up. No statistical comparison between groups reported. Time to first retreatment was 7.3 weeks to 25.4 weeks[20]. **(VERY LOW)** **For ranibizumab vs laser therapy: One RCT provided low certainty evidence of treatment failure in 31% of patients with two different ranibizumab doses and 14% with laser therapy at up to 24 weeks follow-up. A second RCT provided low certainty evidence of treatment failure in 44% of patients with ranibizumab and 4% with laser therapy at up to approximately 12 months follow-up. The RCT groups were not statistically compared. One retrospective cohort study provided very low certainty evidence of no statistically significant difference in treatment failure between ranibizumab and laser therapy at approximately three years follow-up. A second retrospective cohort study provided very low certainty evidence of treatment failure in 67% of patients following ranibizumab and 0% of patients after laser therapy at up to six months follow-up. The groups were not statistically compared.** **For ranibizumab, laser therapy and bevacizumab: Two retrospective cohort studies provided very low certainty evidence of no statistically significant difference in treatment failure between ranibizumab, laser therapy and bevacizumab at approximately three years and 18-20 months follow-up respectively. However, in one of these studies, treatment failure was statistically significantly higher for ranibizumab compared to bevacizumab in multivariable regression analysis.** **For ranibizumab vs bevacizumab: One retrospective cohort study provided very low certainty evidence of treatment failure requiring any retreatment in 14% of patients after ranibizumab and 8% after bevacizumab at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab. This study also reported that statistically significantly more eyes initially treated with ranibizumab required retreatment with anti-VEGF compared to eyes initially treated with bevacizumab.**
Quality of life (QoL) **Certainty of evidence:** Low	Quality of life (for example, Children's Visual Function Questionnaire capturing vision-related QoL or broader standard QoL scales) is important for patients because it gives a measurement of the patient's vision-related quality of life. In total, one extension study from the RAINBOW RCT provided evidence relating to quality of life in infants with ROP at two years follow-up. This study compared ranibizumab and laser therapy. Quality of life was assessed using the Children's

[19] These results are presented as treatment failure due to the absence of any evidence to confirm that retreatment was required after 24 weeks

[20] The time to first retreatment range suggests some infants from the ranibizumab group may have received retreatment post 24 weeks but this number is not reported

Outcome	Evidence statement
	Visual Function Questionnaire (CVFQ)[21] and the Mullen Scales of Early Learning[22]. No evidence was identified relating to quality of life for ranibizumab vs bevacizumab. **At 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported *no statistically significant difference* in quality of life assessed using the CVFQ at age 20-28 months (corrected for prematurity) between two ranibizumab doses (0.2mg n=54; 0.1mg n=50) and laser therapy (n=37). For 0.2mg ranibizumab vs laser therapy mean composite scores were 84 (95%CI 80 to 88) vs 77 (95%CI 72 to 83) (p=0.063). For 0.1mg ranibizumab vs laser therapy mean composite scores were 79 (95%CI 75 to 83) vs laser therapy (as above) (p>0.05). **(LOW)** • One RCT extension study (Marlow et al 2021, RAINBOW) reported median (IQR) T-scores for three subscales of the Mullen Scales of Early Learning at age 20-28 months (corrected for prematurity) for two ranibizumab doses (0.2mg n=56; 0.1mg n=52) and laser therapy (n=43). Visual reception T-scores were 40 (29 to 52) for 0.2mg ranibizumab, 38 (25 to 49) for 0.1mg ranibizumab and 40 (20 to 49) for laser therapy. Receptive language T-scores were 44 (36 to 50) for 0.2mg ranibizumab, 40 (27 to 49) for 0.1mg ranibizumab and 40 (27 to 50) for laser therapy. Expressive language T-scores were 36 (30 to 44) for 0.2mg ranibizumab, 30 (25 to 41) for 0.1mg ranibizumab and 33 (22 to 46) for laser therapy. No statistical comparison between groups reported. **(LOW)** **For ranibizumab vs laser therapy: One RCT extension study provided low certainty evidence of no statistically significant difference in vision-related quality of life at age 20-28 months (corrected for prematurity) between ranibizumab and laser therapy. The same study also reported similar scores for the different groups in an assessment using a scale of early learning but did not statistically compare the groups.**
Retreatment **Certainty of evidence:** Very low	Retreatment (for example, post 24 weeks for ranibizumab or post 4 weeks for diode laser) is important for patients because they may need to come back for more treatment which can be inconvenient for the patient or put them at risk if anaesthesia is needed for treatment. In total, one RCT (RAINBOW), one extension study from the RAINBOW RCT and one retrospective cohort study provided evidence relating to retreatment in infants with ROP for between up to 24 weeks and up to approximately two years follow-up. These studies compared ranibizumab and laser therapy. No evidence was identified for retreatment for ranibizumab vs bevacizumab. **At up to two years:** *Ranibizumab vs laser therapy* • One RCT and RCT extension study (Marlow et al 2021, Stahl et al 2019, RAINBOW) reported that 0/56 patients in the 0.2mg ranibizumab group and 1/53 (1.9%) in the 0.1mg ranibizumab group received retreatment during the extension study, between 24 weeks and up to two years after initial treatment. In addition, 4/74 (5.4%) patients in the laser therapy group received retreatment more than four weeks after their initial treatment. No statistical comparison between groups reported. **(VERY LOW)** **At up to six months:**

[21] The CVFQ for children under 3 years of age is a validated questionnaire with 4 vision-related subscales (competence, personality, family impact and treatment effect), 2 subscales for general health and general vision and a summative composite score. Scores are derived from 5-point Likert-type scales from 1.0 (best possible outcome) to 0.0 (worst possible outcome). Subscale and summary scores are standardised to range from 0 to 100 with higher scores indicating better function/ quality of life

[22] The Mullen Scales of Early Learning assess developmental progress with 3 subscales (visual recognition, receptive language and expressive language). The mean population norm T-score is 50 (SD 10)

Outcome	Evidence statement
	Ranibizumab vs laser therapy • One retrospective cohort study (Chmielarz-Czarnocińska et al 2021) reported that 46/226 eyes (20.4%) from the laser therapy group received retreatment between seven weeks and approximately six months after initial treatment. It is not clear if any ranibizumab group patients received retreatment more than 24 weeks after initial treatment. **(VERY LOW)** **For ranibizumab vs laser therapy: One RCT and RCT extension study provided very low certainty evidence of retreatment for a single patient (1.9%) after 0.1mg ranibizumab and 5% of patients after laser therapy. There were no retreatments after 0.2mg ranibizumab up to approximately two years follow-up. The groups were not statistically compared. A retrospective cohort study provided very low certainty evidence that 20% of eyes that initially received laser therapy had retreatment up to six months after initial treatment. It was not clear if any patients from the ranibizumab group had received retreatment in this study.**
Development of infection **Certainty of evidence:** Low to very low	Development of infection (for example, endophthalmitis) is important for patients because it may lead to permanent blindness. In total, two RCTs and one retrospective cohort study provided evidence relating to development of infection in infants with ROP for between 24 weeks and 18-20 months follow-up. Results comparing ranibizumab and laser therapy were available from the two RCTs. Results comparing ranibizumab, laser therapy and bevacizumab were available from the retrospective cohort study. **At 18 - 20 months:** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported no cases of endophthalmitis for 22 patients after ranibizumab, 55 patients after laser therapy or 57 patients after bevacizumab. Mean follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. **(VERY LOW)** **At approximately 1 year:** *Ranibizumab vs laser therapy* • One RCT (Zhang et al 2017) reported no cases of endophthalmitis in patients who received ranibizumab (n=25) or laser therapy (n=25). Mean ± SD follow-up was 49.94 ± 14.67 weeks for ranibizumab and 54.03 ± 12.40 weeks for laser therapy. **(LOW)** **At 24 weeks:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported endophthalmitis cases at 24 weeks follow-up for two ranibizumab doses (0.2mg 0/73, 0%; 0.1mg 1/76, 1.3%) and laser therapy (0/69, 0%). No statistical comparison between groups reported. **(VERY LOW)** **For ranibizumab vs laser therapy: One RCT provided very low certainty evidence of a single case of endophthalmitis (1.3%) at 24 weeks follow-up after 0.1mg ranibizumab. There were no cases of endophthalmitis after 0.2mg ranibizumab or after laser therapy. The groups were not statistically compared. There were no cases of endophthalmitis in a second RCT comparing ranibizumab and laser therapy up to approximately 12 months follow-up.** **For ranibizumab, laser therapy and bevacizumab: There were no cases of endophthalmitis in a retrospective cohort study comparing ranibizumab, laser therapy and bevacizumab at 18-20 months follow-up.**
Safety	
Adverse events	Adverse events include those relating to VEGF treatment, cataract, treatment-related abnormal neuro-developmental outcomes, serum plasma VEGF outcomes and treatment complications.

Outcome	Evidence statement
Certainty of evidence: Low to very low	In total, two RCTs, one extension study from the RAINBOW RCT and three retrospective cohort studies provided evidence relating to adverse events in infants with ROP for between 29 days and approximately three years follow-up. Results comparing ranibizumab and laser therapy were available from the two RCTs, the RCT extension study and one retrospective cohort study. Results comparing ranibizumab, laser therapy and bevacizumab were available from one retrospective cohort study. Results comparing ranibizumab and bevacizumab were available from one retrospective cohort study. **At 3 years:** *Ranibizumab vs laser therapy* • One retrospective cohort study (Kang et al 2019) reported *no statistically significant difference* between ranibizumab and laser therapy at mean ± SD follow-up of 36.3 ± 31.9 months for the following major complications: vitreous haemorrhage; cataract, pale disc without known neurologic deficits or glaucoma. Vitreous haemorrhage occurred in 2/153 eyes (1.3%) after ranibizumab and 1/161 eyes (5.0%) after laser therapy (p=0.614). Cataract occurred in 1/153 eyes (0.7%) after ranibizumab and 1/161 eyes (0.6%) after laser therapy (p=0.738). Pale disc without known neurologic deficits occurred in 8/153 eyes (5.2%) after ranibizumab and 5/161 eyes (3.1%) after laser therapy (p=0.404). Glaucoma occurred in 0/153 eyes (0%) after ranibizumab and 2/161 eyes (1.2%) after laser therapy (p=0.499). **(VERY LOW)** • Kang et al (2019) also reported no deaths, major systemic complications or adverse neurodevelopmental outcomes at last follow-up with either ranibizumab or laser therapy. **(VERY LOW)** **At 18 months to 2 years:** *Ranibizumab vs laser therapy* • One RCT extension study (Marlow et al 2021, RAINBOW) reported number of adverse ocular events from enrolment in the original 24-week RANIBOW trial up to age 20-28 months (corrected for prematurity) for two ranibizumab doses (0.2mg: 2 (n=74); 0.1mg: 6[23] (n=77)) and laser therapy: 3 (n=74). Number of patients experiencing an adverse event not reported. The most common adverse event was conjunctivitis. No statistical comparison between groups reported. **(LOW)** • Marlow et al (2021) also reported no non-ocular serious adverse events related to the study intervention at last follow-up with either ranibizumab or laser therapy. **(VERY LOW)** *Ranibizumab, laser therapy and bevacizumab* • One retrospective cohort study (Gunay et al 2017) reported no major ocular complications, including iatrogenic cataract or intraocular haemorrhage, after ranibizumab (n=22), laser therapy (n=57) or bevacizumab (n=55). Mean follow-up was 18.96 ± 4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab. **(VERY LOW)** **At approximately 1 year:** *Ranibizumab vs laser therapy* • One RCT (Zhang et al 2017) reported no cases of anterior segment ischemia, pupillary membrane, lens opacity or vitreous haemorrhage after ranibizumab (n=25) or laser therapy (n=25). Mean ± SD follow-up was 49.94 ± 14.67 weeks for ranibizumab and 54.03 ± 12.40 weeks for laser therapy. **(LOW)** *Ranibizumab vs bevacizumab* • One retrospective cohort study (Kang et al 2018) reported *no statistically significant difference* between ranibizumab and bevacizumab at mean ± SD follow-up of 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for

[23] This includes 2 cases of retinal detachment which may have also been included under the structural abnormalities outcome for this study

Outcome	Evidence statement
	bevacizumab for number of cases of the following major complications: vitreous haemorrhage; cataract or pale disc without known neurologic deficits. Vitreous haemorrhage occurred in 1/52 eyes (1.9%) after ranibizumab and 1/101 eyes (1.0%) after bevacizumab (p=0.566). Cataract occurred in 0/52 eyes (0%) after ranibizumab and 1/101 eyes (1.0%) after bevacizumab (p=0.660). Pale disc without known neurologic deficits occurred in 4/52 eyes (7.7%) after ranibizumab and 4/101 eyes (4.0%) after bevacizumab (p=0.445). **(VERY LOW)** • Kang et al (2018) also reported no deaths, major systemic complications or glaucoma cases at last follow-up with either ranibizumab or bevacizumab. **(VERY LOW)** **At up to 24 weeks:** *Ranibizumab vs laser therapy* • One RCT (Stahl et al 2019, RAINBOW) reported number of deaths at 24 weeks follow-up for two ranibizumab doses (0.2mg 4/74, 5.4%; 0.1mg 4/77, 5.2%) and laser therapy (4/74, 5.4%). No statistical comparison between groups reported. **(LOW)** • One RCT (Stahl et al 2019, RAINBOW) reported number of serious ocular adverse events and number of any ocular adverse events at 24 weeks follow-up for two ranibizumab doses and laser therapy. For serious ocular adverse events this was 4/73 (5.5%) for 0.2mg ranibizumab; 1/76 (1.3%) for 0.1mg ranibizumab; and 4/69 (5.8%) for laser therapy. Serious ocular adverse events were ROP (n=6), cataract (n=1), nystagmus[24] (n=1), conjunctivitis (n=1), endophthalmitis (n=1)[25], eye disorder (n=1)) and orbital infection (n=1). For any ocular adverse events this was 22/73 (30.1%) for 0.2mg ranibizumab; 31/76 (40.8%) for 0.1mg ranibizumab; and 23/69 (33.3%) for laser therapy. No statistical comparison between groups reported. **(LOW)** • One RCT (Stahl et al 2019, RAINBOW) reported number of serious non-ocular adverse events and number of any non-ocular adverse events at 24 weeks follow-up for two ranibizumab doses and laser therapy. For serious non-ocular adverse events this was 24/73 (32.9%) for 0.2mg ranibizumab; 24/76 (31.6%) for 0.1mg ranibizumab; and 22/69 (31.9%) for laser therapy. The most common serious non-ocular adverse events (n>5) were pneumonia, bronchiolitis and bronchopulmonary dysplasia. For any non-ocular adverse events this was 62/73 (84.9%) for 0.2mg ranibizumab; 2/76 (81.6%) for 0.1mg ranibizumab; and 53/69 (76.8%) for laser therapy. No statistical comparison between groups reported. **(LOW)** • One RCT (Stahl et al 2019, RAINBOW) reported plasma VEGF up to 29 days follow-up for two ranibizumab doses and laser therapy. In all three groups, levels reduced from day 1 to day 15 and then increased to day 29. Overall, change from day 1 to day 29 was -47 pg/mL for 0.2mg ranibizumab, +10 pg/mL for 0.1mg ranibizumab and -13 pg/mL for laser therapy. No statistical comparison between groups or over time reported. **(LOW)** • One RCT (Stahl et al 2019, RAINBOW) reported serum ranibizumab up to 29 days follow-up for two ranibizumab doses. This outcome was not applicable for laser therapy. For ranibizumab 0.2mg and 0.1mg, levels reduced from day 1 (7,820 and 4,350 pg/mL) to day 15 (4,440 and 3,400 pg/mL) and then reduced further to day 29 (1,070 and 1,060). No statistical comparison over time reported. **(LOW)** **For ranibizumab vs laser therapy: One RCT provided low certainty evidence of serious ocular adverse events in 1% of patients after 0.1mg ranibizumab and 6% after 0.2mg ranibizumab or laser therapy after 24 weeks follow-up. Serious non-ocular adverse events occurred in 32% to 33% of patients for all three groups. Rates of any ocular adverse event were 41% after 0.1mg ranibizumab and 30% and 34% after 0.2mg ranibizumab or laser therapy**

[24] This is also reported under the sight impairment/ severe sight impairment outcome
[25] This is also reported under the development of infection outcome

Outcome	Evidence statement
	respectively. Rates of any non-ocular adverse event were 85% for 0.2mg ranibizumab, 82% for 0.1mg ranibizumab and 77% for laser therapy. The groups were not statistically compared. This RCT also reported plasma VEGF up to 29 days follow-up for two ranibizumab doses and laser therapy. In all three groups, levels reduced from day 1 to day 15 and then increased to day 29. The groups were not statistically compared. For the ranibizumab groups, serum ranibizumab levels reduced from day 1 to day 15 and then further reduced to day 29 (to approximately 1,000 pg/mL in both groups). An extension study to this RCT provided very low certainty evidence of no serious non-ocular adverse events related to the study intervention at last follow-up when patients were approximately two years old (low certainty). A second RCT provided low certainty evidence of no cases of specified ocular adverse events with ranibizumab or laser therapy up to approximately 12 months follow-up. One retrospective cohort study provided very low certainty evidence of no statistically significant difference between ranibizumab and laser therapy for specified major complications up to approximately three years follow-up, with no deaths, major systemic complications or adverse neurodevelopmental outcomes at last follow-up. **For ranibizumab, laser therapy and bevacizumab: One retrospective cohort study provided very low certainty evidence of no major ocular complications with ranibizumab, laser therapy or bevacizumab at 18-20 months follow-up.** **For ranibizumab vs bevacizumab: One retrospective cohort study provided very low certainty evidence of no statistically significant differences between ranibizumab and bevacizumab for specified major complications at a mean follow-up of 14 months for ranibizumab and 31 months for bevacizumab, with no deaths, major systemic complications or glaucoma cases at last follow-up.**
Abbreviations CI: Confidence intervals; CVFQ; Children's Visual Function Questionnaire; g: Grams; IQR: Inter quartile range; kg: Kilogram; mg: Milligram; ml: Millilitres; OR: Odds ratio; pg/mL: Picogram/millilitre; RCT: Randomised controlled trial; ROP: Retinopathy of prematurity; SD: Standard deviation; VEGF: Vascular endothelial growth factor	

In preterm infants, what is the cost effectiveness of ranibizumab as first line drug treatment compared with standard of care for ROP?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of preterm infants that may benefit more from ranibizumab as first line drug treatment than the wider population of interest?

Outcome	Evidence statement
Subgroups	Analysis by disease stage was reported for the critical outcome of high myopia and the important outcomes of treatment failure and safety, with some studies also reporting analysis by patient characteristics. **High Myopia** • One retrospective cohort study (Gunay et al 2017) reported presence of high myopia in a *statistically significantly lower* proportion of patients with Zone I ROP (n=42) who received ranibizumab (14.3%) or bevacizumab (23.8%) compared to laser therapy (71.4%) (p=0.019). There was *no statistically significant difference* in the presence of high myopia in patients with Zone II ROP (n=92) who received ranibizumab (12.5%), laser therapy (6%) or bevacizumab (5.9%) (p=0.773). Mean ± SD follow-up was 18.96 ±

4.79 months for ranibizumab, 20.68 ± 6.89 months for laser therapy and 19.40 ± 6.43 months for bevacizumab.

Treatment failure

- A post-hoc analysis from the RAINBOW RCT (Fleck et al 2022) reported number of eyes receiving additional treatment up to age 20-28 months (corrected for prematurity) by disease stage at baseline. For patients who received 0.2mg ranibizumab this was 8/35 (22.9%) for Zone I, 23/93 (24.7%) for Zone II and 9/20 (45.0%) for AP ROP with a median (range) time to first retreatment of 48.5 days (4 to 111). For patients who received 0.1mg ranibizumab this was 14/39 (35.9%) for Zone I, 12/93 (12.9%) for Zone II and 16/20 (80.0%) for AP ROP with a median (range) time to first retreatment of 48 days (7 to 128). For patients who received laser therapy this was 11/38 (28.9%) for Zone I, 17/90 (18.9%) for Zone II and 6/20 (30.0%) for AP ROP with a median (range) time to first retreatment of 16 days (7 to 141). No statistical comparison between groups or between disease stages reported.
- A retrospective cohort study (Ling et al 2019) with a mean ± SD of 197.3 ± 110 weeks follow-up reported that in multivariable logistic regression analysis, the following were *statistically significant independent risk factors* for treatment failure:
  - Zone I ROP vs Zone II ROP OR 4.444 (95%CI 1.872 to 10.552), p=0.0007
  - Early postmenstrual age at initial treatment OR 0.816 (95%CI 0.692 to 0.963), p=0.0160
  - Low Apgar score OR 0.832 (95%CI 0.705 to 0.982), p=0.0297
  - Multiple births OR 2.285 (95%CI 1.071 to 4.788), p=0.0285
- Ling et al (2019) also reported that in the ranibizumab group, higher risk of recurrent ROP was *statistically significantly* associated with:
  - Early postmenstrual age at initial treatment OR 0.494 (95%CI 0.285 to 0.857), p=0.0121
  - Pneumonia OR 23.582 (95%CI 1.532 to 362.908), p=0.0235
  - Multiple birth OR 17.282 (95%CI 1.171 to 254.963), p=0.0380.

Safety

- A retrospective cohort study (Kang et al 2019) with a mean ± SD follow-up of 36.3 ± 31.9 months reported that in multivariate regression analysis, an initial ROP stage of 3 was associated with a *statistically significantly higher* incidence of major complications (retinal detachment, optic atrophy, cataract) than an initial ROP stage of 2 (OR 11.222 (95%CI 1.883 to 66.788), p=0.008)[26]
- Kang et al (2019) also reported that gestational age and postmenstrual age at initial treatment were *not statistically significantly* associated with the incidence of major complications
- A retrospective cohort study (Kang et al 2018) with a mean ± SD follow-up of 13.9 ± 12.5 months for ranibizumab and 30.9 ± 18.4 months for bevacizumab reported that in univariable analysis, an initial ROP stage of 3 was associated with a *statistically significant higher* incidence of major complications (retinal detachment, optic atrophy, cataract surgery) than an initial ROP stage of 2 (OR 9.046 (95%CI 1.635 to 50.061), p=0.012)
- Kang et al (2018) also reported that there was *no statistically significant association* between major complications and sex, birth weight, gestational age at birth or postmenstrual age at initial treatment.

One retrospective cohort study reported high myopia in statistically significantly fewer patients with Zone I ROP after ranibizumab or bevacizumab compared to laser therapy. There was no statistically significant difference between treatment groups for patients with Zone II ROP. A post-hoc analysis from an RCT reported lower cases of treatment failure for patients who received ranibizumab and had Zone I or Zone II ROP

[26] Birth weight was also described as being statistically significantly associated with the incidence of major complications but the reporting and direction of this result was unclear

	than for patients with aggressive posterior ROP. For patients who received laser therapy, treatment failure cases were lower for Zone II ROP but appeared similar for Zone I and aggressive posterior ROP. However, neither the treatment groups nor disease groups were statistically compared. In a retrospective cohort study, significant independent risk factors for treatment failure included Zone I ROP, early postmenstrual age at initial treatment, low Apgar score, pneumonia and multiple births. In two retrospective cohort studies, an initial ROP stage of 3 was associated with a statistically significant higher incidence of major complications than an initial ROP stage of 2.
Abbreviations AP: Aggressive posterior; CI: Confidence intervals; OR: Odds ratio; RCT: Randomised controlled trial; ROP: Retinopathy of prematurity; SD: Standard deviation	

From the evidence selected, what are the criteria used by the research studies to define those preterm infants diagnosed with ROP who are eligible to receive first line drug treatment with ranibizumab?

Outcome	Evidence statement
Criteria for treatment commencement with ranibizumab	The RAINBOW RCT (Fleck et al 2022, Marlow et al 2021, Stahl et al 2019) included preterm infants (birth weight <1,500g) with bilateral ROP Zone I stage 1+, 2+ 3 or 3+ or Zone II stage 3+ or AP ROP[27]. This RCT excluded infants with ROP in Zone II, stage 2+; ocular and neurological comorbidities that might result in confounding visual impairment and active ocular infection within five days before investigational treatment. The RCT by Zhang et al (2017) screened preterm infants (birth weight <2,000g or birth weight ≥2,000g but with severe systemic disorders) for ROP. Infants with binocular Zone II treatment-requiring ROP (i.e. ROP with Stage 2+ or 3+ in Zone II) were eligible for inclusion. This RCT excluded preterm infants with ROP in Zone I, Stage 4 or Stage 5 ROP and AP ROP in either eye. The retrospective cohort study by Chmielarz-Czarnocińska et al (2021) screened preterm infants (gestational age ≤33 weeks and birth weight <1,800g or high risk as determined by a neonatologist) for ROP. Treatment criteria were based on the ETROP[28] study with some cases also receiving treatment after the acute-phase treatment criteria defined by ETROP at the discretion of the examining ophthalmologist. In this study the authors stated that treatment was determined by the treating ophthalmologist depending on the severity of the disease with ranibizumab preferred for infants with Zone I ROP with plus disease, Zone I ROP stage 3 without plus disease and for AP ROP. In their retrospective cohort study, Gunay et al (2017) stated that decisions to treat infants were made according to the indications established in the ETROP study[28]. This study excluded infants with stage 4 or 5 ROP and infants who received supplemental treatment with intravitreal injections following failed laser therapy. The retrospective cohort studies by Kang et al (2019) and Kang et al (2018) both screened preterm infants (gestational age <32 weeks and birth weight <1,500g or unstable clinical course as determined by the primary neonatologist) for ROP. Infants meeting the treatment criteria had type 1 ROP as defined in the ETROP

[27] In ROP, the three zones refer to specific locations of the eye centred around the optic nerve. Zone I is the innermost area and Zone III the outermost. There are five stages of ROP which relate to the severity of the condition from Stage 1 (mild) to Stage 5 (total retinal detachment). Retinopathy of prematurity - RNIB - See differently. Severe ROP is associated with dilation and tortuosity of the retinal vessels, termed plus disease (International Classification of Retinopathy of Prematurity, Third Edition - Ophthalmology (aaojournal.org))

[28] Early Treatment for Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch. Ophthalmol. 2003;121, 1684–1694

	study[29] with some cases receiving earlier treatment at the discretion of the primary ophthalmologist. In Kang et al (2018) the authors stated that there was a gradual change in preference from bevacizumab to ranibizumab over the study period due to reports of safer systemic profiles for ranibizumab. In their retrospective cohort study, Ling et al (2020) stated that indications for treatment were infants whose retinopathy met the criteria of Type I ROP in the BEAT-ROP study[30].
Abbreviations AP: Aggressive posterior; BEAT-ROP: Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity; ETROP: Early Treatment for Retinopathy of Prematurity; g: Grams; RCT: randomised controlled trial; ROP: retinopathy of prematurity; VEGF	

[29] Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-48

[30] The reference for the BEAT-ROP study given by the study authors is the same as the reference for the ETROP study provided by Chmielarz-Czarnocińska et al (2021) and Gunay et al 2017

6. Discussion

This evidence review considered the clinical effectiveness and safety of ranibizumab compared to standard care for the treatment of ROP in preterm infants. The critical outcomes of interest were unfavourable structural retinal outcomes, high myopia and sight impairment/ severe sight impairment. Important outcomes were treatment failure, quality of life, retreatment, development of infection and adverse events. Evidence on cost effectiveness was also sought.

Evidence was available from two RCTs, one of which (RAINBOW) also had results from an extension study, and five retrospective cohort studies. The RCTs and two retrospective cohort studies compared ranibizumab and laser therapy. Two retrospective cohort studies compared ranibizumab, laser therapy and bevacizumab. One retrospective cohort study compared ranibizumab and bevacizumab. No studies were identified comparing ranibizumab to cryotherapy or argon laser.

The RAINBOW RCT was a multi-centre study (87 centres) conducted in 26 countries. Three of the 87 centres were in the UK with five of the 225 patients randomised from the UK centres. The authors stated that 40% of the randomised infants came from a geographical region with infant mortality of at least five per 1,000 births and 60% from a geographical region with infant mortality of less than five per 1,000 births, with the UK being in this latter group. The other studies were conducted in one or two centres in China, Poland, South Korea, Taiwan and Turkey. It is not clear to what extent the results of these studies might be generalisable to the UK population.

All studies included preterm infants with ROP. Inclusion criteria relating to prematurity varied with birth weights specified ranging from less than 1,500g to less than 2,000g. Age, when specified, was less than 32 weeks or 33 weeks or less. One RCT (Zhang et al 2017) was limited to infants with Zone II ROP (stage 2+ or stage 3+) and infants with aggressive posterior ROP in either eye were excluded. The RAINBOW RCT included infants with Zone II ROP if they were stage 3+ but also included infants with Zone I ROP and infants with aggressive posterior ROP. All five of the retrospective cohort studies based their inclusion criteria on the ETROP study. Treatment was also permitted for infants outside of the specified criteria, for example, if there were also severe systemic disorders or at the discretion of the clinical specialist.

In three of the five retrospective cohort studies, the decision about which treatment to have was made by the infant's parents/ guardians. In the other cohort studies treatment was determined by the treating ophthalmologist depending on the severity of the disease (Chmielarz-Czarnocińska et al 2021) or there was a gradual change in preference from bevacizumab to ranibizumab over the time period covered by the study (Kang et al 2018). One of the retrospective cohort studies (Ling et al 2020) stated that the groups were similar at baseline. However, in the remaining four retrospective cohort studies this was unclear. The similarity between groups at baseline was also unclear in one of the RCTs (RAINBOW). The dose of ranibizumab used in the studies ranged from 0.1mg to 0.3mg but was either 0.2mg or 0.25mg in most studies.

The RAINBOW RCT included between 74 and 77 patients in each of the three groups. The initial power calculation was revised down to 60 per group at 80% power due to slow enrolment and recruitment challenges. The primary outcome reported by the RAINBOW RCT was a composite outcome for treatment success (defined by survival without active ROP, unfavourable structural outcomes or the need for a treatment modality other than that assigned). This composite outcome was not an outcome of interest specified for this review. Although appropriate statistical analysis was undertaken for the primary outcome, the authors stated that because a statistically significant difference was not observed for the

primary outcome, significance testing for the other outcomes reported was not undertaken. Statistical comparison of treatment groups was undertaken in the RAINBOW RCT extension study, however only 68% of the patients randomised in the original RCT were included in these analyses. The RCT by Zhang et al (2017) included 25 patients in each group and did not report details of any power calculation. Although this RCT did conduct statistical comparison of the study groups, this was not for outcomes of interest specified for this review. For example, the authors compared rates of recurrence, regardless of whether the recurrence required further treatment. Although recurrence requiring retreatment was also reported for the two groups, and included in this review, this outcome was not statistically compared. The retrospective cohort studies included between 83 and 176 patients with more patients receiving the comparator treatment than ranibizumab in all studies.

Follow-up of patients ranged from approximately six months to more than three years. The extension study from the RAINBOW RCT is due to follow-up patients for five years. However, only the results of the planned two year interim analysis have been reported to date. The follow-up duration was generally sufficient for the outcomes reported in the studies however, it was often unclear if follow-up was complete. Outcomes relating to high myopia and quality of life were available for patients up to approximately two years of age. Follow-up to an older age would be of value for these outcomes and data on visual acuity up to five years of age will be available from the final results of the RAINBOW extension study.

It would not have been practical to blind patients or clinicians to the RCT treatment groups due to the differences in delivery methods. It is possible that the lack of blinding may introduce a potential bias for self-reported measures. However, it is unlikely to impact the objective outcomes reported. Outcome assessors were not blinded to treatment assignment although this would have been possible. The authors of the RAINBOW RCT noted that decisions on retreatment were made on an individual basis and that clinician preference for one treatment could have led to biased decisions to re-treat. In the RCT by Zhang et al (2019), more patients in the ranibizumab group received a crossover treatment although any impact for the outcomes of interest to this review was not clear.

Evidence comparing ranibizumab and laser therapy was identified for all outcomes. No data on ranibizumab compared to bevacizumab was identified for the important outcomes of quality of life or retreatment. The effectiveness and safety outcomes reported by studies, including the RCTs, often lacked statistical analysis comparing treatment groups. Many of the outcomes of interest for this review represented unfavourable events that could occur such as structural abnormalities, infections, impaired vision or adverse events. In several instances, studies specified that no unfavourable events occurred for the outcomes of interest. No information about what any minimal clinically important thresholds or differences might be was reported for any of the outcomes considered.

Limitations reducing certainty in the RAINBOW RCT outcomes included uncertainty about differences between the groups at baseline and in the way the two groups were treated, incomplete follow-up and uncertainty about whether ‘unfavourable structural retinal outcomes’ were measured in a reliable way. Limitations reducing certainty in a second RCT included differences in the way the two groups were treated. Limitations reducing certainty in the retrospective cohort studies included lack of clarity about the similarity between the groups at baseline for all but one of the five studies, lack of adjustment for potential confounding factors and uncertainty about whether follow-up was complete. For all studies, additional uncertainty for some outcomes included lack of statistical analysis, lack of blinding for subjective outcomes and imprecision because no events occurred for some outcomes.

Several studies considered results for patient subgroups with different ROP disease stages. However, it is difficult to draw conclusions as the results were reported differently across the studies; sometimes characterised as a comparison between Zone I and Zone II ROP, sometimes as a comparison between stage 2 and stage 3 ROP or just as a descriptive breakdown of results for different disease stages. One study investigated specified patient characteristics (early postmenstrual age at initial treatment, low Apgar score, pneumonia and multiple births) as potential risk factors for treatment failure.

7. Conclusion

This evidence review includes two RCTs, one RCT extension study and five retrospective cohort studies with comparisons between ranibizumab and either laser therapy or bevacizumab. The populations of all studies were infants with ROP. No evidence was identified comparing ranibizumab to cryotherapy or argon laser.

There was data from RCTs and an RCT extension study on the number of cases of outcomes with ranibizumab or laser therapy for the critical outcomes of unfavourable structural retinal outcomes and sight impairment/ severe sight impairment. These generally reported lower numbers of these unfavourable outcomes with ranibizumab, particularly at a dose of 0.2mg when different doses were used in the RCT. However, they did not provide any statistical analysis comparing the treatment groups. Statistical comparison of treatment groups for the critical outcomes of unfavourable structural retinal outcomes, high myopia and sight impairment/ severe sight impairment was available from an RCT extension study and/ or retrospective cohort studies. For these critical outcomes, the statistical analyses either reported no statistically significant difference between ranibizumab and laser therapy or bevacizumab or reported results that favoured ranibizumab.

There was data from RCTs, without statistical comparison of the treatment groups, on the number of cases for the important outcome of treatment failure. Both RCTs reported a higher number of cases of treatment failure with ranibizumab than laser therapy. In three retrospective cohort studies that conducted statistical comparison of treatment groups, there was no statistically significant difference in treatment failure between ranibizumab, laser therapy and bevacizumab. However, there was some evidence of statistically significantly more cases of treatment failure for ranibizumab compared to bevacizumab in two studies. Limited evidence was identified for retreatment, with no comparison of treatment groups for this important outcome. For the important outcome of quality of life, one RCT extension study reported no statistically significant difference between ranibizumab and laser therapy. No studies reporting quality of life for ranibizumab compared to bevacizumab were identified. For the important outcome of development of infection, only one case was reported across the three studies that reported this outcome, suggesting that this outcome rarely occurs with ranibizumab, laser therapy or bevacizumab.

For safety outcomes, numbers of serious ocular and non-ocular adverse events appeared to be similar with ranibizumab and laser therapy within one RCT but the groups were not statistically compared. Two retrospective cohort studies that conducted statistical comparison of treatment groups reported no statistically significant difference in major complications between ranibizumab and laser therapy or bevacizumab.

Limitations reducing certainty in the evidence identified included uncertainty about the similarity of groups at baseline and in the way the two groups were treated, incomplete or uncertain follow-up, lack of adjustment for potential confounding factors and, for one outcome, uncertainty about whether this were measured in a reliable way, lack of statistical analysis, lack of blinding for subjective outcomes and imprecision because no events occurred for some outcomes.

There was limited evidence that patients with Zone I ROP might benefit from ranibizumab or bevacizumab more than laser therapy in terms of high myopia and, in a post-hoc analysis from an RCT, there appeared to be lower cases of treatment failure for patients who received ranibizumab and had Zone I or Zone II ROP rather than aggressive posterior ROP based on a descriptive report of number of cases. However, Zone I ROP was a significant risk factor for treatment failure, compared to Zone II ROP in a retrospective cohort study

along with early postmenstrual age at initial treatment, low Apgar score, pneumonia and multiple births. An initial ROP stage of 3 was associated with a higher incidence of major complications than an initial ROP stage of 2 in two retrospective cohort studies.

The studies identified for this review therefore provide moderate to very low certainty evidence that overall, for preterm infants with ROP there may be little difference in effectiveness and safety for ranibizumab compared to laser therapy or bevacizumab. Where studies did report a statistical advantage for one treatment, this favoured ranibizumab for unfavourable structural retinal outcomes, high myopia and sight impairment/ severe sight impairment, but not for treatment failure.

Appendix A PICO Document

The review questions for this evidence review are:

1. In preterm infants, what is the clinical effectiveness of ranibizumab as first line drug treatment compared with standard of care for ROP?

2. In preterm infants, what is the safety of ranibizumab as first line drug treatment compared with standard of care for ROP?

3. In preterm infants, what is the cost effectiveness of ranibizumab as first line drug treatment compared with standard of care for ROP?

4. From the evidence selected, are there any subgroups of preterm infants that may benefit more from ranibizumab as first line drug treatment than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define those preterm infants diagnosed with ROP who are eligible to receive first line drug treatment with ranibizumab?

P-Population and Indication	• Preterm infants with ROP
	[this may include infants for whom laser treatment cannot be administered, due to media opacity, equipment failure, small pupils or other factors; or where infants are unstable and may not tolerate laser or sedation; or infants for whom laser treatment has failed]
	• Subgroups of interest include
	  ○ infants with very posterior disease [defined as Zone I, Zone II posterior or A-ROP]
	  ○ infants for whom laser treatment has failed

I-Intervention	Intravitreal ranibizumab as first line drug treatment
C-Comparator	Standard of care[31]: • Diode laser (retinal photocoagulation) • Cryotherapy • Argon laser • Bevacizumab
O-Outcomes	**<u>Clinical Effectiveness</u>** [Please note that outcomes may be reported in terms of number of eyes or number of children] **Critical for decision making** • Unfavourable structural retinal outcomes [such as substantial temporal retinal vessel dragging causing structural features or macular ectopia; or retrolental membrane obscuring the posterior pole, posterior retinal fold, or retinal detachment involving the macula] *This outcome is important for patients because they can all contribute to poor vision or blindness* • High myopia [for example <-5 Dioptres] *This outcome is important for patients because this contributes to patients being dependent on glasses. Glasses are essential to*

[31] In the UK 2022 ROP treatment guideline of Royal College Ophthalmologists, cryotherapy is not recommended, and green wavelength laser (which includes Argon) is regarded as equivalent to diode laser (https://www.rcophth.ac.uk/resources-listing/uk-retinopathy-of-prematurity-guideline/)

	wear during the child's "critical period" of development up to 7 years. It can be difficult for many patients to wear glasses earlier than this age and non-compliance with not wearing them can lead to a "lazy eye" (amblyopia). • Sight impairment/ severe sight impairment [for example irreversible sight impairment outcomes such as amblyopia which cannot be treated. High myopia which does not lead to amblyopia would not overlap as it is treatable with glasses] *This outcome is important for patients because this is a disability and may restrict many activities and occupations for the patient later in life.* **Important for decision making** [Please note that retreatment following ranibizumab may be with the same or an alternative treatment] • Treatment failure [for example retreatment within 24 weeks for ranibizumab, or within 4 weeks for diode laser] *This outcome is important for patients because they may need to come back for more treatment which can be inconvenient for the patient or put them at risk if anaesthesia is needed for treatment*. • Quality of life (QoL) [for example Children's Visual Function Questionnaire capturing vision-related quality of life or broader standard QoL scales] *This outcome is important for patients because it gives a measurement of the patient's vision-related quality of life* • Retreatment: [for example post 24 weeks for ranibizumab, or post 4 weeks for diode laser] *This outcome is important for patients because they may need to come back for more treatment which can be inconvenient for the patient or put them at risk if anaesthesia is needed for treatment* • Development of infection [for example endophthalmitis] *This outcome is important for patients because it may lead to permanent blindness.* **Safety** • Adverse events including those relating to VEGF treatment, cataract, treatment-related abnormal neuro-developmental outcomes, serum plasma VEGF outcomes, and treatment complications **Cost effectiveness** • Cost per QALY • Cost per DALY
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2012-2022
Exclusion criteria	

Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines.
Study design	Case reports, resource utilisation studies.

Appendix B Search strategy

Medline, Embase, the Cochrane Library, the NHS Knowledge and Library Hub and the TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2012 to 18 March 2022

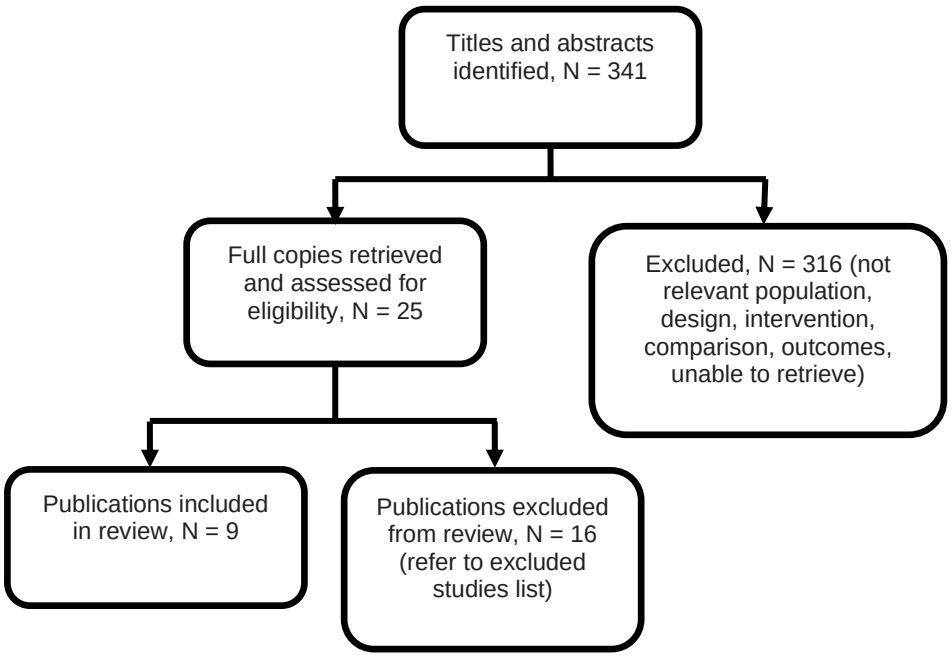
Medline search strategy:

1	Retinopathy of Prematurity/
2	((preterm or pre-term or prematur*) adj3 retinopath*).ti,ab,kw.
3	((preterm or pre-term or prematur*) and (retrolental adj3 fibroplasia*)).ti,ab,kw.
4	1 or 2 or 3
5	Ranibizumab/
6	(ranibizumab or lucentis or accentrix or byooviz).ti,ab,kw.
7	5 or 6
8	4 and 7
9	limit 8 to (english language and yr="2012 -Current")

Appendix C Evidence selection

The literature search identified 341 potential references. These were screened using their titles and abstracts and 25 references potentially relating to the use of ranibizumab for ROP were obtained in full text and assessed for relevance. Of these, nine references are included in this evidence review. The 16 references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Stahl A, Lepore D, Fielder A, Fleck B, Reynolds JD, Chiang MF, Li J, Liew M, Maier R, Zhu Q, Marlow N. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. Lancet. 2019;394(10208):1551-9.	Included in the review
Marlow N, Stahl A, Lepore D, Fielder A, Reynolds JD, Zhu Q, Weisberger A, Stiehl DP, Fleck B. 2-year outcomes of ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW extension study): prospective follow-up of an open label, randomised controlled trial. The Lancet Child & Adolescent Health. 2021;5(10):698-707.	Included in the review
Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. New England Journal of Medicine. 2011;364:603-15.	Excluded. This was published outside of the search dates specified in the PICO (appendix A)

Appendix D Excluded studies table

Study reference	Reason for exclusion
Alyamac Sukgen E, Comez A, Kocluk Y, Cevher S. The Process of Retinal Vascularization after Anti-VEGF Treatment in Retinopathy of Prematurity: A Comparison Study between Ranibizumab and Bevacizumab. Ophthalmologica. 2016;236(3):139-47.	Retrospective comparison of ranibizumab and bevacizumab (n=45). Larger studies of same design and outcomes available.
Barry GP, Yu Y, Ying GS, Tomlinson LA, Lajoie J, Fisher M, et al. Retinal Detachment after Treatment of Retinopathy of Prematurity with Laser versus Intravitreal Anti-Vascular Endothelial Growth Factor. Ophthalmology. 2021;128(8):1188-96.	The anti-VEGF group combines ranibizumab and bevacizumab. Ranibizumab only 17/164 eyes and not separately reported.
Beccasio A, Mignini C, Caricato A, Iaccheri B, Di Cara G, Verrotti A, et al. New trends in intravitreal anti-VEGF therapy for ROP. European Journal of Ophthalmology. 2022:11206721211073405.	Descriptive review of several different anti-VEGF drugs.
Chen SN, Lian I, Hwang YC, Chen YH, Chang YC, Lee KH, et al. Intravitreal anti-vascular endothelial growth factor treatment for retinopathy of prematurity: comparison between Ranibizumab and Bevacizumab. Retina. 2015;35(4):667-74.	Retrospective comparison of ranibizumab and bevacizumab (n=37). Larger studies of same design and outcomes available.
Chen YC, Chen SN, Yang BC, Lee KH, Chuang CC, Cheng CY. Refractive and Biometric Outcomes in Patients with Retinopathy of Prematurity Treated with Intravitreal Injection of Ranibizumab as Compared with Bevacizumab: A Clinical Study of Correction at Three Years of Age. Journal of ophthalmology. 2018;2018:4565216.	Retrospective comparison of ranibizumab and bevacizumab (n=33). Larger studies of same design and outcomes available.
Iwahashi C, Utamura S, Kuniyoshi K, Sugioka K, Konishi Y, Wada N, et al. Factors Associated with Reactivation after Intravitreal Bevacizumab or Ranibizumab Therapy in Infants with Retinopathy of Prematurity. Retina. 2021;41(11):2261-8.	Retrospective comparison of ranibizumab and bevacizumab (n=43). Larger studies of the same design and outcomes available.
Kabatas EU, Kurtul BE, Altiaylik Ozer P, Kabatas N. Comparison of Intravitreal Bevacizumab, Intravitreal Ranibizumab and Laser Photocoagulation for Treatment of Type 1 Retinopathy of Prematurity in Turkish Preterm Children. Current Eye Research. 2017;42(7):1054-8.	Has separate results for ranibizumab, bevacizumab and laser. But small numbers of bevacizumab (12) and ranibizumab (6). Also a fourth group of patients who spontaneously regressed. The statistical comparisons are mainly across all 4 groups. Have studies comparing ranibizumab to just the PICO comparators for these outcomes.
Kang HG, Kim TY, Han J, Han SH. Refractive Outcomes of 4-Year-old Children after Intravitreal Anti-vascular Endothelial Growth Factor versus Laser Photocoagulation for Retinopathy of Prematurity. Korean Journal of Ophthalmology. 2019;33(3):272-8.	Retrospective comparison with anti-VEGF group that combines bevacizumab (90%) and ranibizumab (10%). No separate results for ranibizumab.
Kimyon S, Mete A. Comparison of Bevacizumab and Ranibizumab in the Treatment of Type 1 Retinopathy of Prematurity Affecting Zone 1. Ophthalmologica. 2018;240(2):99-105.	Retrospective comparison of ranibizumab and bevacizumab (n=37). Larger studies of same design and outcomes available.
Pertl L, Steinwender G, Mayer C, Hausberger S, Poschl EM, Wackernagel W, et al. A systematic review and meta-analysis on the safety of vascular endothelial growth factor (VEGF) inhibitors for the treatment of retinopathy of prematurity. PLoS ONE. 2015;10(6) (no pagination).	Results relating to ranibizumab only descriptive reporting. Individual studies considered separately.
Popovic MM, Nichani P, Muni RH, Mireskandari K, Tehrani NN, Kertes PJ. Intravitreal antivascular endothelial growth factor injection versus laser photocoagulation for retinopathy of prematurity: A meta-analysis of 3,701 eyes. Survey of Ophthalmology. 2021;66(4):572-84.	Meta-analysis pools anti-VEGF agents. Individual studies considered separately.
Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. Cochrane Database of Systematic Reviews. 2018;1:CD009734.	Only includes one ranibizumab study (Zhang et al 2017). This study is separately included.
Suren E, Ozkaya D, Cetinkaya E, Kalayci M, Yigit K, Kucuk MF, et al. Comparison of bevacizumab, ranibizumab and aflibercept in	Comparison reported is across 3 anti-VEGFs (ranibizumab, bevacizumab and

retinopathy of prematurity treatment. International Ophthalmology. 2022;30:30.	aflibercept). Have studies comparing ranibizumab to just the PICO comparators for these outcomes.
VanderVeen DK, Melia M, Yang MB, Hutchinson AK, Wilson LB, Lambert SR. Anti-Vascular Endothelial Growth Factor Therapy for Primary Treatment of Type 1 Retinopathy of Prematurity: A Report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(5):619-33.	No meta-analysis. Includes 2 ranibizumab studies (Gunay et al 2017; Zhang et al 2017). These studies are separately included.
Wang SD, Zhang GM, Shenzhen Screening for Retinopathy of Prematurity Cooperative G. Laser therapy versus intravitreal injection of anti-VEGF agents in monotherapy of ROP: a Meta-analysis. International Journal of Ophthalmology. 2020;13(5):806-15.	Meta-analysis pools anti-VEGF agents. Individual studies considered separately.
Zhang C, Reynolds AL, Beiter A, Lillvis JH, Reynolds JD. Effect of Low-dose Intravitreal Bevacizumab and Ranibizumab on Regression and Late Reactivation in Retinopathy of Prematurity in the Treatment-Naive Eyes. Ophthalmology Retina. 2021;27:27.	Retrospective comparison of ranibizumab and bevacizumab (n=20). Larger studies of the same design and outcomes available.

Appendix E Evidence Table

For abbreviations see list after table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Chmielarz-Czarnocińska A, Pawlak M, Szpecht D, Choręziak A, Szymankiewicz-Bręborowicz M, Gotz-Więckowska A. Management of retinopathy of prematurity (ROP) in a Polish cohort of infants. Scientific Reports. 2021;11(1):4522. **Study location** Single-centre, Poland **Study type** Retrospective cohort study **Study aim** To analyse the results of ROP treatment from a centre in Poland **Study dates** January 2016 to December 2019	Preterm infants with ROP **Inclusion criteria** Preterm infants (gestational age ≤33 weeks and birth weight <1,800g or high risk as determined by a neonatologist) were screened for ROP. Treatment criteria were based on the ETROP[32] study with some cases also receiving treatment after the acute-phase treatment criteria defined by ETROP at the discretion of the examining ophthalmologist **Exclusion criteria** None stated **Total sample size** n=178 preterm infants (350 eyes)	**Intervention** Intravitreal injection of ranibizumab under general anaesthesia as a single dose of 0.25mg/0.025mL **Comparison** Laser therapy delivered under general anaesthesia No details of any concomitant treatments reported	Mean follow-up not reported **Important outcomes** Time to first retreatment ranged from 51 days (7.3 weeks) to 178 days (25.4 weeks). Time to retreatment not separately reported for treatment groups. However, the lower and upper end of the ranges suggest that most of the additional treatments received by the ranibizumab group fall within the PICO definition of treatment failure for ranibizumab (i.e. within 24 weeks) and all the additional treatments received by the laser therapy group fall within the PICO definition of retreatment for laser therapy (i.e. >4 weeks) **Treatment failure** Number (%) of eyes with recurrence of ROP requiring any additional treatment: • Ranibizumab: 80/120 (66.7%) • Laser therapy: 0/226 (0%) No statistical comparison between groups for any additional treatment **Retreatment** • Ranibizumab: not reported • Laser therapy: 46/226 (20.4%)	This study was appraised using the JBI checklist for cohort studies: 1. Unclear 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Unclear 9. Unclear 10. Unclear 11. No **Other comments** This was a retrospective study describing the management and outcomes of preterm infants treated for ROP at 1 centre. Baseline characteristics were not separately reported or compared for the different treatment groups. Treatment decisions were made by the treating ophthalmologist depending on

[32] Early Treatment for Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch. Ophthalmol. 2003;121, 1684–1694

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Ranibizumab: n=61 (120 eyes) Laser therapy: n=115 (226 eyes) In addition, 2 infants received simultaneous laser therapy and ranibizumab (results not extracted) ROP disease stage for infants born and treated at the study centre (n=108): Zone I, stage 1-: 0% Zone I, stage 1+: 3.8% Zone I, stage 2-: 0.9% Zone I, stage 2+: 1.9% Zone I, stage 3-: 0.9% Zone I, stage 3+: 3.8% Zone II, stage 1-: 0.9% Zone II, stage 1+: 4.2% Zone II, stage 2-: 6.1% Zone II, stage 2+: 20.3% Zone II, stage 3-: 11.8% Zone II, stage 3+: 34.9% Aggressive posterior ROP: 10.4% Disease stage not reported for 70 patients who received primary neonatal care at other hospitals **Baseline characteristics**		The time to first retreatment range suggests some infants from the ranibizumab group may have received retreatment post 24 weeks but this number is not reported	disease severity with ranibizumab preferred for some disease stages. It is therefore not clear that the groups were similar at baseline. The authors considered disease stage as a potentially confounding factor but did not adjust for any potential confounding factors. Mean follow-up was not reported. It is not clear if follow-up was complete or of sufficient duration. No statistical analysis comparing treatment groups was reported. The outcome reported was objective. Although the time range for retreatment was reported, this was for the whole study population rather than for the different treatment groups. This resulted in difficulty assigning the results according to the distinction between treatment failure and retreatment as defined in the PICO. The authors stated that retinal detachment was observed in 14 eyes (4%) in 7 patients, but this

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Study population (n=178): Gestational age at birth in weeks (mean ± SD): 26 ± 2 (range 22 to 31) Birth weight g (mean ± SD): 868 ± 236 (range 410 to 1,890) Baseline characterises not separately reported for infants who received laser therapy or ranibizumab No comparison of baseline characteristics for the treatment groups. The authors stated that treatment was determined by the treating ophthalmologist depending on the severity of the disease, with ranibizumab preferred for infants with Zone I ROP with plus disease, Zone I ROP stage 3 without plus disease and for aggressive posterior ROP			was not separately reported for the different treatment groups. The study was conducted in 1 centre in Poland over a 3 year period. The generalisability of the results to the NHS in England is unclear. Results for the 2 infants who received simultaneous laser therapy and ranibizumab were not extracted as this is not an intervention of interest. **Source of funding:** The authors stated that the research received no external funding and that there were no competing interests.
Fleck BW, Reynolds JD, Zhu Q, Lepore D, Marlow N, Stahl A, Li J, Weisberger A, Fielder AR on behalf of the RAINBOW investigator group. Time course of	Preterm infants with ROP This is a post-hoc analysis of data from the RAINBOW RCT. See Stahl et al 2019 for the trial inclusion/	This is a post-hoc analysis of data from the RAINBOW RCT. There were 2 intervention groups in the RCT where patients received	Outcomes reported up to 2 years follow-up **Important outcomes** **Treatment failure** *Number (%) of eyes that received additional treatment by disease stage at baseline*	This paper reports the outcome of treatment failure reported in the original RAINBOW trial broken down by disease stage (see Stahl et al 2019) and the interim 2-year analysis (see Marlow et al 2021)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

retinopathy of prematurity regression and reactivation after treatment with ranibizumab or laser in the RAINBOW trial. Ophthalmology Retina. 2022;21:21.
 	
Study location
Multi-centre, 26 countries
 	
Study type
Post-hoc analysis from an RCT
 	
Study aim
To assess the time course of ROP regression and reactivation for participants in an RCT evaluating the efficacy and safety of ranibizumab compared to laser therapy for the treatment of ROP
 	
Study dates
December 2015 to January 2018
	exclusion criteria and baseline characteristics
	
	For the population included in this post-hoc analysis:
	
	Total sample size
	n=225 preterm infants (448 eyes)
	
	Ranibizumab 0.2mg: n=74 (148 eyes)
	Ranibizumab 0.1mg: n=77 (152 eyes)
	Laser: n=74 (148 eyes)
	
	Zone I ROP:
	• Ranibizumab 0.2mg: 35 eyes
	• Ranibizumab 0.1mg: 39 eyes
	• Laser: 38 eyes
	
	Zone II ROP:
	• Ranibizumab 0.2mg: 93 eyes
	• Ranibizumab 0.1mg: 93 eyes
	• Laser: 90 eyes
	
	Aggressive posterior ROP:
	• Ranibizumab 0.2mg: 20 eyes
		either 0.2mg or 0.1mg ranibizumab. The comparator was laser therapy. See Stahl et al 2019 for further details	• Ranibizumab 0.2mg:
			Median (range) time to first additional treatment: 48.5 days (4 to 111)
			By disease stage:
			  • Zone I: 8/35 (22.9%)
			  • Zone II: 23/93 (24.7%)
			  • Aggressive posterior ROP: 9/20 (45.0%)
			• Ranibizumab 0.1mg:
			Median (range) time to first additional treatment: 48 days (7 to 128)
			By disease stage:
			  • Zone I: 14/39 (35.9%)
			  • Zone II: 12/93 (12.9%)
			  • Aggressive posterior ROP: 16/20 (80.0%)
			• Laser therapy:
			Median (range) time to first additional treatment: 16 days (7 to 141)
			By disease stage:
			  • Zone I: 11/38 (28.9%)
			  • Zone II: 17/90 (18.9%)
			  • Aggressive posterior ROP: 6/20 (30.0%)
			
			No statistical analysis between treatment groups or disease stages
				The RAINBOW RCT and extension study were critically appraised using the JBI checklist for RCTs. See Stahl et al 2019 and Marlow et al 2021 for further details.
				
				Other comments
				In this subgroup analysis, treatment failure is reported for number of eyes broken down by disease stage.
				
				Patients who received retreatment at any time during the core trial or extension study are included in this analysis. For ranibizumab it is possible to infer whether additional treatments should be considered as treatment failure (defined as retreatment within 24 weeks) or retreatment (post 24 weeks for ranibizumab based on the duration of the study follow-up periods reported in different analyses. However, the distinction between the definitions for treatment failure and retreatment for laser therapy is based on whether this took place within or after 4 weeks from the initial treatment. The treatment range reported for laser therapy suggests that

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Ranibizumab 0.1mg: 20 eyes • Laser: 20 eyes			some treatments took place after 4 weeks but this number is not known. The results reported in this analysis are presented as treatment failure based on the median time interval between initial treatment and first additional treatment. **Source of funding:** The study was funded by Novartis Pharma AG. The authors stated that employees of the funding organisation participated in the design, conduct, data collections, data management, data analysis and interpretation of the data and preparation, review and approval of the manuscript.
Gunay M, Sukgen EA, Celik G, Kocluk Y. Comparison of Bevacizumab, Ranibizumab, and Laser Photocoagulation in the Treatment of Retinopathy of Prematurity in Turkey. Current Eye Research. 2017;42(3):462-9. **Study location**	Preterm infants with ROP **Inclusion criteria** Decisions to treat infants were made according to the indications established in the ETROP[33] study **Exclusion criteria** Infants with stage 4 or 5 ROP. Infants who received supplemental	**Intervention** Intravitreal injection of ranibizumab under topical anaesthesia as a single dose of 0.25mg/0.025mL **Comparison** Laser therapy delivered under topical anaesthesia	Mean ± SD follow-up (months): • Ranibizumab: 18.96 ± 4.79 (range 16.83 to 21.08) • Laser therapy: 20.68 ± 6.89 (range 18.85 to 22.50) • Bevacizumab: 19.40 ± 6.43 (range 17.66 to 21.14) p=0.602 **Critical outcomes** **Unfavourable structural retinal outcomes**	This study was appraised using the JBI checklist for cohort studies: 1. Unclear 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Unclear

[33] Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-48

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
2 centres, Turkey **Study type** Retrospective cohort study **Study aim** To evaluate the efficacies and treatment outcomes of ranibizumab, bevacizumab and laser therapy for ROP **Study dates** December 2012 to August 2014	treatment with intravitreal injections following failed laser therapy **Total sample size** n=134 preterm infants (264 eyes) Ranibizumab: n=22 Laser therapy: n=57 Bevacizumab: n=55 Number of eyes in each group not reported Zone I ROP: 13.3% Zone II ROP: 68.7% Aggressive posterior ROP: 18.7% **Baseline characteristics** *Ranibizumab* Male: 59.1% Gestational age at birth in weeks (mean ± SD): 27.95 ± 2.9 (range 26.69 to 29.24) Birth weight g (mean ± SD): 1,195.90 ± 466.98 (range 938.85 to 1,190.69) Postmenstrual age at treatment in weeks (mean ± SD): 35.59 ± 1.58 (range 34.89 to 36.29) Zone I ROP: 63.6%	Intravitreal injection under topical anaesthesia of bevacizumab as a single dose of 0.625mg/0.025mL Patients receiving ranibizumab or bevacizumab received topical antibiotics for 1 week after treatment Patients receiving laser therapy received steroid-antibiotic drops for 1 week after treatment	Unfavourable anatomical outcomes were any of: dragging of the disc, localised tractional or non-tractional membranes at posterior pole or in the retinal periphery and total or partial retinal detachment: • Ranibizumab: 0/22 (0%) • Laser therapy: 1/57 (1.8%) • Bevacizumab: 0/55 (0%) The 1 unfavourable outcome was a stable 4A retinal detachment No statistical comparison between groups **High myopia** Presence of high myopia (≤ -5.0 Dioptres) (%): • Ranibizumab: 13.6% • Laser therapy: 14% • Bevacizumab: 12.7% No statistically significant differences between groups (p=0.979) Number of infants experiencing high myopia in each group not reported Presence of high myopia (%) for infants with Zone I ROP (n=42): • Ranibizumab: 14.3% • Laser therapy: 71.4% • Bevacizumab: 23.8% p=0.019 for laser therapy compared to ranibizumab and bevacizumab Presence of high myopia (%) for infants with Zone II ROP (n=92): • Ranibizumab: 12.5%	10. Unclear 11. Yes **Other comments** This retrospective study compared outcomes for preterm infants who received ranibizumab, laser therapy, or bevacizumab as the primary treatment for ROP at 2 centres. There were some differences between the groups at baseline. The authors stated that the parents were given the decision about which treatment their child received. The impact on the results is not clear. The authors considered potentially confounding factors such as disease stage but did not adjust for any potential confounding factors in analysis of the outcomes of interest. The outcomes reported were objective. Mean follow-up was reported, but it is not clear if follow-up was complete. The study was conducted in 2 centres in Turkey over a 2 year period. The generalisability of

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Zone II ROP: 36.4% Aggressive posterior ROP: 40.1% *Laser therapy* Male: 56.1% Gestational age at birth in weeks (mean ± SD): 28.23 ± 2.50 (range 27.57 to 28.89) Birth weight g (mean ± SD): 1,119.47 ± 336.96 (range 1,014.63 to 1,179.05) Postmenstrual age at treatment in weeks (mean ± SD): 36.03 ± 1.41 (range 35.65 to 36.39) Zone I ROP: 12.3% Zone II ROP: 87.7% Aggressive posterior ROP: 1.8% *Bevacizumab* Male: 38.2% Gestational age at birth in weeks (mean ± SD): 27.31 ± 2.18 (range 26.72 to 27.90) Birth weight g (mean ± SD): 1,005.29 ± 411.19 (range 894.13 to 1,116.45) Postmenstrual age at treatment in weeks (mean		• Laser therapy: 6% • Bevacizumab: 5.9% No statistically significant differences between groups (p=0.773) **Important outcomes** **Treatment failure** • Ranibizumab: 3/22 (13.6%) Time to retreatment (mean ± SD): 8.75 ± 1.5 weeks • Laser therapy: 0/57 (0%) • Bevacizumab: 3/55 (5.5%) Time to retreatment (mean ± SD): 14 ± 2.65 weeks No statistically significant differences between groups (p=0.098) **Development of infection** The authors reported that there were no cases of endophthalmitis in any of the groups **Safety** The authors reported that there were no cases of major ocular complications in any of the groups, including iatrogenic cataract or intraocular haemorrhage	the results to the NHS in England is unclear. **Source of funding:** No statement was made about funding. The authors reported no conflicts of interest.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	± SD): 34.75 ± 1.91 (range 34.23 to 35.27) Zone I ROP: 38.2% Zone II ROP: 61.8% Aggressive posterior ROP: 27.2% The groups were similar in terms of gestational age and birth weight. There was a statistically significant difference in postmenstrual age at treatment (p=0.001) and there was a statistically significantly higher percentage of patients with Zone II ROP in the laser therapy group (p=0.001)			
Kang HG, Choi EY, Byeon SH, Kim SS, Koh HJ, Lee SC, Kim M. Intravitreal ranibizumab versus laser photocoagulation for retinopathy of prematurity: efficacy, anatomical outcomes and safety. British Journal of Ophthalmology. 2019;103(9):1332-6. **Study location** 1 centre, South Korea	Preterm infants with ROP **Inclusion criteria** Preterm infants (gestational age <32 weeks and birth weight <1,500g or unstable clinical course as determined by the primary neonatologist) were screened for ROP. Infants meeting the treatment criteria had type 1 ROP as defined in the	**Intervention** Intravitreal injection of ranibizumab under topical anaesthesia as a single dose of 0.25mg/ 0.025mL **Comparison** Laser therapy delivered under general anaesthesia No details of any concomitant treatments reported	Mean ± SD follow-up (months): 36.3 ± 31.9 **Critical outcomes** **Unfavourable structural retinal outcomes** *Retinal detachment* Number (%) of eyes with retinal detachment: • Ranibizumab: 1/153 (0.7%) • Laser therapy: 8/161 (5.0%) p=0.037 Number (%) of eyes with temporal macular dragging: • Ranibizumab: 1/153 (0.7%) • Laser therapy: 7/161 (4.3%)	This study was appraised using the JBI checklist for cohort studies: 1. Unclear 2. Yes 3. Yes 4. Yes 5. Unclear 6. Yes 7. Yes 8. Yes 9. No 10. No 11. Yes

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study type Retrospective cohort study **Study aim** To compare the efficacy, anatomical outcomes and complications of intravitreal ranibizumab and laser photocoagulation for ROP **Study dates** January 2006 to December 2016	ETROP[34] study with some cases receiving earlier treatment at the discretion of the primary ophthalmologist **Exclusion criteria** Infants with follow-up of less than 12 months, infants lost to follow-up **Total sample size** n=165 preterm infants (314 eyes) Ranibizumab: 153 eyes Laser therapy: 161 eyes Number of patients in each treatment group not reported Zone I ROP: 16.2% Zone II ROP: 72.3% Zone III ROP: 11.5% Stage 2 ROP: 10.2% Stage 3 ROP: 89.8% Aggressive posterior ROP: 7.2% Presence of + disease: 66.6%		p=0.039 **Sight impairment/ severe sight impairment** Number (%) of eyes that had strabismus operation[35]: • Ranibizumab: 21/153 (13.7%) • Laser therapy: 26/161 (16.1%) No statistically significant difference between groups (p=0.636) **Important outcomes** **Treatment failure** Number (%) of eyes with recurrence of ROP requiring any additional treatment: • Ranibizumab: 15/153 (9.8%) Mean time to retreatment 5.7 weeks • Laser therapy: 22/161 (13.7%) Mean time to retreatment 2.3 weeks No statistically significant difference between groups (p=0.196) **Safety** *Major complications* Number (%) of eyes with vitreous haemorrhage • Ranibizumab: 2/153 (1.3%) • Laser therapy: 1/161 (0.6%) No statistically significant difference between groups (p=0.614)	**Other comments** This retrospective study compared outcomes for preterm infants who received ranibizumab or laser therapy for ROP at 1 centre. There were some differences between the groups at baseline. The authors stated that treatment modality was chosen after careful discussion with the infant's guardians. The impact on the results is not clear. The authors considered potentially confounding factors such as disease stage. No details of any adjustments for multivariate analysis were reported. It is not clear if adjustment for any potential confounding factors was made. The outcomes reported were mainly objective. The assessment of any adverse neurodevelopmental outcomes was determined by review of medical records and routine use

[34] Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-48

[35] Strabismus is a squint, where the eyes point in different directions. If untreated in young children, lazy eye (amblyopia) can develop with poor vision in the eye with the squint (Squint (strabismus) - Moorfields Eye Hospital)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Baseline characteristics *Ranibizumab* Male: 54.2% Gestational age at birth in weeks (mean ± SD): 27.3 ± 2.5 Birth weight g (mean ± SD): 1,049.2 ± 411.1 PMA at treatment in weeks (mean ± SD): 40.0 ± 2.5 Zone I ROP: 22.2% Zone II ROP: 69.9% Zone III ROP: 7.8% Stage 2 ROP: 10.5% Stage 3 ROP: 89.5% Aggressive posterior ROP: 7.2% Presence of + disease: 57.5% *Laser therapy* Male: 51.6% Gestational age at birth in weeks (mean ± SD): 28.8 ± 10.3 Birth weight in g (mean ± SD): 1,012.0 ± 301.1 PMA at treatment (mean ± SD): 43.1 ± 15.3 Zone I ROP: 10.6% Zone II ROP: 74.5% Zone III ROP: 14.9%		Number (%) of eyes with cataract: • Ranibizumab: 1/153 (0.7%) • Laser therapy: 1/161 (0.6%) No statistically significant difference between groups (p=0.738) Number (%) of eyes with pale disc without known neurologic deficits: • Ranibizumab: 8/153 (5.2%) • Bevacizumab: 5/161 (3.1%) No statistically significant difference between groups (p=0.404) Number (%) of eyes with glaucoma: • Ranibizumab: 0/153 (0%) • Laser therapy: 2/161 (1.2%) No statistically significant difference between groups (p=0.499) There were no deaths or major systemic complications in either group. There were no adverse neurodevelopmental outcomes in either group In multivariate regression analysis, an initial ROP stage of 3 was associated with a statistically significant higher incidence of major complications (retinal detachment, optic atrophy, cataract) than an initial ROP stage of 2 (OR 11.222 (95%CI 1.883 to 66.788), p=0.008)[36]	of the Denver II Developmental Screening Test. Infants with follow-up of less than 12 months and 6 infants lost to follow-up were excluded. The number of infants who received treatment during this period but were excluded due to a follow-up period of less than 12 months is not clear. The study was conducted in 1 centre in South Korea over a 10 year period. The generalisability of the results to the NHS in England is unclear. **Source of funding:** The paper states that the authors have not declared a specific grant for the research from any funding agency in the public, commercial or non-for-profit sectors. No competing interests declared.

[36] Birth weight was also described as being statistically significantly associated with the incidence of major complications but the reporting and direction of this result was unclear

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Stage 2 ROP: 9.9% Stage 3 ROP: 90.1% Aggressive posterior ROP: 0% Presence of + disease: 75.2% The groups were similar for sex, body weight and gestational age. The postmenstrual age at primary treatment was higher for the laser therapy group (p=0.012). There were statistically significantly more Zone I (22% vs 11%, p=0.006) and aggressive posterior ROP cases (7% vs 0%, p<0.001) in the ranibizumab group		Primary treatment type, gestational age and postmenstrual age at initial treatment were not statistically significantly associated with the incidence of major complications	
Kang HG, Choi EY, Byeon SH, Kim SS, Koh HJ, Lee SC, Kim, M. Anti-vascular Endothelial Growth Factor Treatment of Retinopathy of Prematurity: Efficacy, Safety, and Anatomical Outcomes. Korean Journal of Ophthalmology. 2018;32(6):451-8. **Study location**	Preterm infants with ROP **Inclusion criteria** Preterm infants (gestational age <32 weeks and birth weight <1,500g or unstable clinical course as determined by the primary neonatologist) were screened for ROP. Infants who met the criteria for treatment had type 1 ROP as defined in the	**Intervention** Bilateral intravitreal injection of ranibizumab under topical anaesthesia as a single dose of 0.2mg/0.02mL **Comparison** Bilateral intravitreal injection under topical anaesthesia of bevacizumab as a single dose of 0.625mg/0.025mL	Mean follow-up (months): • Ranibizumab: 13.9 ± 12.5 • Bevacizumab: 30.9 ± 18.4 p<0.001 **Critical outcomes** **Unfavourable structural retinal outcomes** *Retinal detachment* Number (%) of eyes with retinal detachment • Ranibizumab: 0/52 (0%) • Bevacizumab: 1/101 (1.0%) No statistically significant difference between groups (p=0.660)	This study was appraised using the JBI checklist for cohort studies: 1. Unclear 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Unclear 10. Unclear 11. Yes

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
2 centres, South Korea **Study type** Retrospective cohort study **Study aim** To investigate the efficacy, safety and anatomical outcomes associated with intravitreal anti-VEGF treatment of ROP using ranibizumab and bevacizumab **Study dates** June 2011 to January 2017	ETROP[37] study with some cases receiving earlier treatment at the discretion of the primary ophthalmologist **Exclusion criteria** None stated **Total sample size** n=83 preterm infants (153 eyes) Ranibizumab: 52 eyes Bevacizumab: 101 eyes Number of patients in each treatment group not reported Zone I ROP: 22.2% Zone II ROP: 69.9% Zone III ROP: 7.8% Aggressive posterior ROP: 7.2% **Baseline characteristics** *Ranibizumab* Male: 40.4%	No details of any concomitant treatments reported	*Temporal macular dragging* Number (%) of eyes with temporal macular dragging: • Ranibizumab: 1/52 (1.9%)[38] • Bevacizumab: 0/101 (0%) No statistically significant difference between groups (p=0.340) **Sight impairment/ severe sight impairment** Number (%) of eyes that had strabismus operation[39]: • Ranibizumab: 0/52 (0%) • Bevacizumab: 21/101 (20.8%) p<0.001 **Important outcomes** **Treatment failure** Number (%) of eyes with recurrence of ROP requiring any additional treatment: • Ranibizumab: 7/52 (13.5%) • Bevacizumab: 8/101 (7.9%) Time to retreatment not reported No statistical comparison between groups for any additional treatment Number (%) of eyes requiring an additional anti-VEGF injection:	**Other comments** This retrospective study compared outcomes for preterm infants who received ranibizumab or bevacizumab for ROP at 2 centres. There were some differences between the groups at baseline. The authors stated that there was a gradual change in preference from bevacizumab to ranibizumab over the study period due to reports of safer systemic profiles for ranibizumab. The impact on the results is not clear. The authors considered potentially confounding factors such as disease stage. It is not clear that adjustment for any potential confounding factors was made. The outcomes reported were objective. No timeframe was provided for retreatment. These

[37] Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-48

[38] There is a discrepancy in the paper about whether the one infant with temporal macular dragging received bevacizumab or ranibizumab. The result from the data table (rather than the text) is reported here

[39] Strabismus is a squint, where the eyes point in different directions. If untreated in young children, lazy eye (amblyopia) can develop with poor vision in the eye with the squint (Squint (strabismus) - Moorfields Eye Hospital)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Gestational age at birth in weeks (mean ± SD): 28.1 ± 3.2 Birth weight g (mean ± SD): 1,257.7 ± 514.5 PMA at treatment in weeks (mean ± SD): 39.2 ± 2.3 Zone I ROP: 40.4% Zone II ROP: 55.8% Zone III ROP: 3.8% Stage 2 ROP: 19.2% Stage 3 ROP: 80.8% Aggressive posterior ROP: 11.5% Presence of + disease: 55.8% *Bevacizumab* Male: 61.4% Gestational age at birth in weeks (mean ± SD): 26.9 ± 1.9 Birth weight g (mean ± SD): 941.8 ± 296.1 PMA at treatment in weeks (mean ± SD): 40.4 ± 2.4 Zone I ROP: 12.9% Zone II ROP: 77.2% Zone III ROP: 9.9% Stage 2 ROP: 5.9% Stage 3 ROP: 94.1% Aggressive posterior ROP: 5.0%		• Ranibizumab: 7/52 (13.5%) • Bevacizumab: 4/101 (4.0%) p=0.037 **Safety** *Major complications* Number (%) of eyes with vitreous haemorrhage • Ranibizumab: 1/52 (1.9%) • Bevacizumab: 1/101 (1.0%) No statistically significant difference between groups (p=0.566) Number (%) of eyes with cataract: • Ranibizumab: 0/52 (0%) • Bevacizumab: 1/101 (1.0%) No statistically significant difference between groups (p=0.660) Number (%) of eyes with pale disc without known neurologic deficits: • Ranibizumab: 4/52 (7.7%) • Bevacizumab: 4/101 (4.0%) No statistically significant difference between groups (p=0.445) There were no cases or glaucoma or “known systemic complications (e.g. death)” In univariable analysis, an initial ROP stage of 3 was associated with a statistically significant higher incidence of major complications (retinal detachment, optic atrophy, cataract surgery) than an initial ROP stage of 2 (OR 9.046 (95%CI 1.635 to 50.061), p=0.012)	results are presented as treatment failure due to the absence of any evidence to confirm that retreatment was required after 24 weeks Mean follow-up was reported but was statistically significantly longer for infants who received bevacizumab. It is not clear if follow-up was complete. The study was conducted in 2 centres in South Korea over a 6 year period. The generalisability of the results to the NHS in England is unclear. **Source of funding:** No statement was made regarding funding. The authors stated that there were no potential conflicts of interest

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Presence of + disease: 65.3% Mean gestational age was statistically significantly higher for ranibizumab vs bevacizumab, p=0.013. Mean body weight was also statistically significantly higher for ranibizumab (p<0.001). There was a higher proportion of eyes with Zone I ROP (p<0.001) and stage 2 ROP (p=0.022) for ranibizumab. There was a higher proportion of eyes with Zone II ROP (p=0.009) and stage 3 ROP (p=0.022) for bevacizumab		There was no statistically significant association between major complications and treatment modality, sex, birth weight, gestational age at birth or postmenstrual age at initial treatment	
Ling KP, Liao PJ, Wang NK, Chao AN, Chen KJ, Chen TL, Hwang YS, Lai CC, Wu WC. Rates and Risk Factors for Recurrence of Retinopathy of Prematurity after Laser or Intravitreal Anti-Vascular Endothelial Growth Factor	Preterm infants with ROP **Inclusion criteria** Indications for treatment were infants whose retinopathy met the criteria of Type I ROP as proposed by the BEAT-ROP study[40] **Exclusion criteria**	**Intervention** Intravitreal injection of ranibizumab as a single dose of 0.25mg/0.025mL **Comparison** Laser therapy delivered under sedation	Mean ± SD follow-up: 197.3 ± 110 weeks **Critical outcomes** **Unfavourable structural retinal outcomes** Number (%) of eyes that progressed to retinal detachment • Ranibizumab: 1/48 (2.1%) • Laser therapy: 3/61 (4.9%) • Bevacizumab: 2/231 (0.9%)	This study was appraised using the JBI checklist for cohort studies: 1. Yes 2. Yes 3. Yes 4. Yes 5. Unclear 6. Yes 7. Yes

[40] Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684– 1694

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Monotherapy. Retina. 2020;40(9):1793-803. **Study location** 1 centre, Taiwan **Study type** Retrospective cohort study **Study aim** To determine the rates and risk factors of recurrent ROP treated by laser photocoagulation, ranibizumab or bevacizumab **Study dates** March 2010 to February 2017	Infants with follow-up to less than 75 weeks postmenstrual age **Total sample size** n=176 preterm infants (340 eyes) Ranibizumab: n=25 (48 eyes) Laser therapy: n=33 (61 eyes) Bevacizumab: n=118 (231 eyes) Zone I ROP: 11.1% Zone II ROP: 88.9% **Baseline characteristics** *Ranibizumab* Male: 56.0% Gestational age at birth in weeks (mean ± SD): 26.2 ± 1.6 Birth weight g (mean ± SD): 827.9 ± 187.3 Postmenstrual age at treatment in weeks (mean ± SD): 36.0 ± 3.1 Zone I ROP: 10.4% Zone II ROP: 89.6% Stage 2 ROP: 12.5% Stage 3 ROP: 87.5%	Intravitreal injection of bevacizumab as a single dose of 0.625mg/0.025mL No details of any concomitant treatments reported	No statistically significant differences between groups (p=0.2701) **Important outcomes** **Treatment failure** Number (%) of eyes with recurrence of ROP requiring retreatment • Ranibizumab: 10/48 (20.8%) Time to recurrence (mean ± SD): 8.3 ± 1.6 weeks • Laser therapy: 11/61 (18.0%) Time to recurrence (mean ± SD): 3.6 ± 1.4 weeks • Bevacizumab: 23/231 (10.0%) Time to recurrence (mean ± SD): 8.8 ± 3.9 weeks No statistically significant differences between groups (p=0.0528) For laser therapy, the distinction between treatment failure and retreatment in the PICO is whether retreatment took place before or after 4 weeks from initial treatment. The mean and SD time to recurrence for laser therapy suggests that some infants received retreatment post 4 weeks but this number is not reported In multivariable logistic regression analysis, the following were statistically significant independent risk factors for recurrent ROP[41]: • Ranibizumab vs bevacizumab OR 2.922 (95%CI 1.179 to 7.240), p=0.0205	8. Yes 9. No 10. No 11. Yes **Other comments** The groups were similar for all baseline demographic and ROP characteristics. The authors stated that the final decision about which treatment to have was made by parents. A range of potential risk factors for recurrence were investigated. Multivariable logistic regression analysis conducted but no statement was made about whether this was adjusted for any factors. The outcomes reported were objective. Retreatment following laser therapy is presented as treatment failure based on the mean time to recurrence. However, the SD suggests that an unknown number of infants receiving laser therapy will have had retreatment post 4 weeks. Only infants with follow-up of at least 75 weeks were included in

[41] In this study, all patients who had recurrent ROP received additional treatment

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Laser therapy Male: 60.6% Gestational age at birth in weeks (mean ± SD): 26.5 ± 2.2 Birth weight g (mean ± SD): 902.4 ± 214.0 Postmenstrual age at treatment in weeks (mean ± SD): 36.3 ± 2.9 Zone I ROP: 11.5% Zone II ROP: 88.5% Stage 2 ROP: 6.6% Stage 3 ROP: 93.4% *Bevacizumab* Male: 56.8% Gestational age at birth in weeks (mean ± SD): 26.4 ± 2.3 Birth weight g (mean ± SD): 851.6 ± 242.9 Postmenstrual age at treatment in weeks (mean ± SD): 36.2 ± 2.6 Zone I ROP: 11.7% Zone II ROP: 88.3% Stage 2 ROP: 14.7% Stage 3 ROP: 85.3% The groups were similar for all baseline demographic and ROP characteristics		• Zone I ROP vs Zone II ROP OR 4.444 (95%CI 1.872 to 10.552), p=0.0007 • Early PMA at initial treatment OR 0.816 (95%CI 0.692 to 0.963), p=0.0160 • Low Apgar score OR 0.832 (95%CI 0.705 to 0.982), p=0.0297 • Multiple births OR 2.285 (95%CI 1.071 to 4.788), p=0.0285 In the ranibizumab group, higher risk of recurrent ROP was statistically significantly associated with: • Early postmenstrual age at initial treatment OR 0.494 (95%CI 0.285 to 0.857), p=0.0121 • Pneumonia OR 23.582 (95%CI 1.532 to 362.908), p=0.0235 • Multiple birth OR 17.282 (95%CI 1.171 to 254.963), p=0.0380	the analysis. The authors stated that 176 of 225 infants (78%) who received treatment during the study period were eligible for inclusion in this study. The study was conducted in 1 centre in Taiwan over a 7 year period. The generalisability of the results to the NHS in England is unclear. **Source of funding:** The study was supported by Chang Gung Memorial Hospital Research Grants and the Ministry of Science and Technology Research Grants. The authors stated that they did not have any conflicting interests to disclose and that the sponsors had no role in the design or conduct of the research
Marlow N, Stahl A, Lepore D, Fielder A,	Preterm infants with ROP	This is an extension to the RAINBOW	Infants were assessed at age 20-28 months (corrected for prematurity)	This study was appraised using the JBI checklist for RCTs.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Reynolds JD, Zhu Q, Weisberger A, Stiehl DP, Fleck B. 2-year outcomes of ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW extension study): prospective follow-up of an open label, randomised controlled trial. The Lancet Child & Adolescent Health. 2021;5(10):698-707. **Study location** Multi-centre, 26 countries **Study type** RCT extension study **Study aim** To assess outcomes at 2 years of age for participants in an RCT extension study evaluating the efficacy and safety of ranibizumab compared to laser therapy for the treatment of ROP	This is an extension to the RAINBOW RCT. See Stahl et al 2019 for the trial inclusion/ exclusion criteria and baseline characteristics **Total sample size** n=153 (306 eyes) (extension study) Ranibizumab 0.2mg: n=56 (112 eyes) Ranibizumab 0.1mg: n=53 (106 eyes) Laser: n=44 (88 eyes) The authors stated that key clinical and disease characteristics at enrolment in the RAINBOW trial were similar for those evaluated at 2 years to those in the original trial	RCT. There were 2 intervention groups in the RCT where patients received either 0.2mg or 0.1mg ranibizumab. The comparator was laser therapy See Stahl et al 2019 for further details One infant received a study treatment during this period of the extension study. This infant, from the 0.1mg ranibizumab group, received a second retreatment with ranibizumab	**Critical outcomes** **Unfavourable structural retinal outcomes** (see Stahl et al 2019 for outcome definition) No child developed new structural abnormalities subsequent to the original trial Structural abnormalities present at the age 20-28 months evaluation: • Ranibizumab 0.2mg: 1/56 (1.8%) • Ranibizumab 0.1mg: 1/51 (2.0%) • Laser therapy: 4/44 (9.1%) No structural abnormality for ranibizumab 0.2mg vs laser therapy: OR 5.68 (95%CI 0.60 to 54), p=0.10 No structural abnormality for ranibizumab 0.1mg vs laser therapy: OR 4.82 (95%CI 0.52 to 45), p=0.14 **High myopia** (Defined as ≤-5 dioptres) *Number of patients with high myopia in at least 1 eye:* • Ranibizumab 0.2mg: 4/55 (7.3%) • Laser therapy: 14/41 (34.1%) Ranibizumab 0.2mg vs laser therapy: OR 0.15 (95%CI 0.05 to 0.50), p=0.0021 Not reported for ranibizumab 0.1mg *Number of eyes with high myopia:*	Questions relating to the design of the original RAINBOW RCT are assessed in Stahl et 2019: 1. See Stahl et al 2019 2. See Stahl et al 2019 3. See Stahl et al 2019 4. See Stahl et al 2019 5. See Stahl et al 2019 6. Unclear 7. Unclear 8. No 9. Yes 10. Yes 11. Yes 12. Yes 13. See Stahl et al 2019 **Other comments** This extension study reports the results of a pre-specified 2-year interim analysis. The extension study is designed to follow infants to 5 years of age. All infant ages at assessment were corrected for prematurity. Assessments were completed by local investigators. It is not clear if they were blinded to treatment group. Infants could receive additional treatments (see Stahl et al 2019). One infant received a

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study dates June 2016 to January 2018			• Ranibizumab 0.2mg: 5/110 (4.5%) • Ranibizumab 0.1mg: 8/98 (8.2%) • Laser therapy: 16/82 (19.5%) *Prevalence of high myopia per eye, corrected for within-individual correlation:* Ranibizumab 0.2mg vs laser therapy: OR 0.19 (95%CI 0.05 to 0.69), p=0.012 Ranibizumab 0.1mg vs laser therapy: OR 0.44 (95%CI 0.14 to 1.32), p=0.14 **Sight impairment/ severe sight impairment** Number (%) of patients with an ocular abnormality in one or both eyes *Nystagmus*[42] • Ranibizumab 0.2mg: 2/55 (3.6%) • Ranibizumab 0.1mg: 3/50 (6.0%) • Laser therapy: 5/41 (12.2%) *Strabismus*[43] • Ranibizumab 0.2mg: 11/55 (20.0%) • Ranibizumab 0.1mg: 12/49 (24.5%) • Laser therapy: 13/41 (31.7%) *Abnormal fixation (not further defined)* • Ranibizumab 0.2mg: 1/55 (1.8%) • Ranibizumab 0.1mg: 8/52 (15.4%) • Laser therapy: 2/44 (14.5%)	study treatment during this period of the extension study. Of 201 infants that completed the original RAINBOW RCT, 180 were enrolled in the extension study and 153 (76.1%) were evaluated at 20-28 months old. This represents 68% of the 225 infants originally randomised in the RAINBOW RCT. Of the 27 infants who withdrew from the extension study, 6 were lost to follow-up, 6 were withdrawn, 2 died (unrelated to the trial intervention) and 13 were outside the age range for assessment. Outcomes were objective or assessed using standard measures. The CVFQ was completed by parents. Other outcomes were assessed by trained local assessors. The authors stated that the extension study was not powered for any outcome

[42] Nystagmus is a rhythmical, repetitive and involuntary movement of the eyes which the patient has no control over. There is no cure for nystagmus and sight problems are common (Nystagmus | Great Ormond Street Hospital (gosh.nhs.uk)). However, it is also possible to have this condition with normal or near normal vision

[43] Strabismus is a squint, where the eyes point in different directions. If untreated in young children, lazy eye (amblyopia) can develop with poor vision in the eye with the squint (Squint (strabismus) - Moorfields Eye Hospital). However, it is also possible to have this condition with normal or near normal vision

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Abnormal pupil reaction (not further defined) • Ranibizumab 0.2mg: 0/55 (0%) • Ranibizumab 0.1mg: 3/52 (6.0%) • Laser therapy: 1/42 (2.4%) **Important outcomes** **Quality of life** *Children's Visual Function Questionnaire*[44] (completed by the parents of 141 infants) Composite vision-related quality of life score (mean): • Ranibizumab 0.2mg (n=54): 84 (95%CI 80 to 88) • Ranibizumab 0.1mg (n=50): 79 (95%CI 75 to 83) • Laser therapy (n=37): 77 (95%CI 72 to 83) Ranibizumab 0.2mg vs laser: p=0.063 Ranibizumab 0.1mg vs laser: p>0.05 The authors stated that none of the comparisons between groups were statistically significant for any of the CVFQ subscales (figures displayed graphically)	assessed at the 2-year interim analysis. The confidence intervals around some of the odds ratios reported were very wide reducing confidence in the results. **Source of funding:** The study was funded by Novartis Pharma AG. The authors stated that the funder of the study had full access to and were involved in data collection, data analysis and data interpretation and was involved in the writing of the manuscript and the decision to submit.

[44] The CVFQ for children under 3 years of age is a validated questionnaire with 4 vision-related subscales (competence, personality, family impact and treatment effect), 2 subscales for general health and general vision and a summative composite score. Scores are derived from 5-point Likert-type scales from 1.0 (best possible outcome) to 0.0 (worst possible outcome). Subscale and summary scores are standardised to range from 0 to 100 with higher scores indicating better function/ quality of life

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Mullen Scales of Early Learning[45] (data available for 151 infants) Visual reception T-score (median, IQR): • Ranibizumab 0.2mg (n=56): 40 (29 to 52) • Ranibizumab 0.1mg (n=52): 38 (25 to 49) • Laser therapy (n=43): 40 (20 to 49) Receptive language T-score (median, IQR): • Ranibizumab 0.2mg (n=56): 44 (36 to 50) • Ranibizumab 0.1mg (n=52): 40 (27 to 49) • Laser therapy (n=43): 40 (27 to 50) Expressive language T-score (median, IQR): • Ranibizumab 0.2mg (n=56): 36 (30 to 44) • Ranibizumab 0.1mg (n=52): 30 (25 to 41) • Laser therapy (n=43): 33 (22 to 46) No statistical comparison of groups reported for this measure. The authors stated that the scores were similar in the 3 treatment groups before or following adjustment for potential confounders (no further detail) but did not report these data **Retreatment** Retreatment during extension study (>24 weeks after initial treatment): • Ranibizumab 0.2mg: 0/56 (0%) • Ranibizumab 0.1mg: 1/53 (1.9%) • Laser therapy: 0/44 (0%)	

[45] The Mullen Scales of Early Learning assess developmental progress with 3 subscales (visual recognition, receptive language and expressive language). The mean population norm T-score is 50 (SD 10)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			No statistical comparison between groups 4/74 patients in the laser therapy group received retreatment (>4 weeks after initial treatment) in the original trial period (see Stahl et al 2019) **Safety** Adverse events were reported from enrolment in the original RANIBOW trial (n=225) up to the 2 year interim analysis *Adverse ocular events:* • Ranibizumab 0.2mg (n=74): 2 Including: • Swelling of eyelid or eyelid injury: 1 • Conjunctivitis: 1 • Ranibizumab 0.1mg (n=77): 6 Including: • Conjunctivitis: 2 • Retinal detachment: 2 • Lenticular opacities: 1 • Pustular rash: 1 • Laser therapy (n=74): 3 Including: • Conjunctivitis: 3 The retinal detachment cases were considered serious adverse events, Both originally occurred during the original RAINBOW trial and would have also been included in the numbers of patients experiencing unfavourable structural retinal outcomes Number of patients experiencing an adverse event(s) not reported	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			No statistical comparison between groups *Non-ocular serious adverse events* No non-ocular severe adverse events were considered related to the study intervention by the investigators. Events included common childhood illnesses (e.g. bronchiolitis and pneumonia) and were described as similarly distributed across the treatment groups	
Stahl A, Lepore D, Fielder A, Fleck B, Reynolds JD, Chiang MF, Li J, Liew M, Maier R, Zhu Q, Marlow N. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. Lancet. 2019;394(10208):1551-9. **Study location** Multi-centre (87 centres), 26 countries (Japan (16 centres; 29 patients), US (12;21),	Preterm infants with ROP **Inclusion criteria** Preterm infants (birth weight <1,500g) with bilateral ROP Zone I stage 1+, 2+ 3 or 3+ or Zone II stage 3+ or aggressive posterior ROP **Exclusion criteria** Preterm infants with ROP in Zone II, stage 2+; ocular and neurological comorbidities that might result in confounding visual impairment and active ocular infection within 5 days before investigational treatment; unilateral cases in which	**Intervention** Group 1: Bilateral intravitreal injection of ranibizumab as a single dose of 0.2mg Group 2: Bilateral intravitreal injection of ranibizumab as a single dose of 0.1mg Up to 2 additional treatments with ranibizumab were allowed in each eye at a minimum of 28-day intervals **Comparison**	Outcomes reported up to 24 weeks after treatment **Critical outcomes** **Unfavourable structural retinal outcomes** These included structural abnormalities that have potential effects on visual acuity: retrolental membrane obscuring the view of the posterior pole, substantial temporal retinal vessel dragging causing abnormal structural features or macular ectopia, posterior retinal fold involving the macula, or retinal detachment involving the macula • Ranibizumab 0.2mg: 1/74 (1.4%) • Ranibizumab 0.1mg: 5/77 (6.5%) • Laser therapy: 7/74 (9.5%) No statistical comparison between groups **Sight impairment** Number (%) of patients with nystagmus[47]	This study was appraised using the JBI checklist for RCTs: 1. Yes 2. Yes 3. Unclear 4. No 5. No 6. No 7. Unclear 8. No 9. Yes 10. Yes 11. Unclear 12. No 13. Yes **Other comments** This was an open-label superiority, multi-centre RCT comparing 2 doses of ranibizumab and laser therapy.

[47] Nystagmus is a rhythmical, repetitive and involuntary movement of the eyes which the patient has no control over. There is no cure for nystagmus and sight problems are common (Nystagmus | Great Ormond Street Hospital (gosh.nhs.uk)). However, it is also possible to have this condition with normal or near normal vision

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

India (6;29), Turkey (6;14), Russia (5;20), Italy (4;14), Austria (3;6), Czech Republic (3;9), Greece (3;10), Romania (3;16), UK (3;5), Belgium (2;10), Croatia (2;9), France (2;3), Germany (2;3), Hungary (2;2), Malaysia (2;2), Poland (2;3), Taiwan (2;7), Denmark (1;1), Egypt (1;3), Estonia (1;2), Lithuania (1;1), Mexico (1;6), Saudi Arabia (1;1), Slovakia (1;1))
 	
Study type
RCT
 	
Study aim
To evaluate the efficacy and safety of ranibizumab compared to laser therapy for the treatment of ROP
 	
Study dates
	only one eye met treatment criteria
	
	Total sample size
	n=225 preterm infants (448 eyes[46])
	
	Ranibizumab 0.2mg: n=74 (148 eyes)
	Ranibizumab 0.1mg: n=77 (152 eyes)
	Laser: n=74 (148 eyes)
	
	Zone I ROP: 86 (38.2%)
	Zone II ROP: 138 (61.3%)
	Aggressive posterior ROP: 30 (13.3%)
	
	Baseline characteristics
	Ranibizumab 0.2mg
	Male: 45%
	Gestational age in weeks (median, range): 25 (23 to 32)
	Birth weight g (mean ± SD): 791 ± 244
	Postmenstrual age at treatment in weeks (median, range): 36.7 (30.3 to 51.9)
		Laser therapy administered according to local protocols
		
		Supplementary laser treatment to skip lesions was allowed up to day 11
		
		No details of any concomitant treatments reported
			• Ranibizumab 0.2mg: 1/73 (1.4%)
			• Ranibizumab 0.1mg: 0/76 (0%)
			• Laser therapy: 0/69 (0%)
			No statistical comparison between groups
			
			Important outcomes
			
			Treatment failure
			Number (%) of patients who received additional post-baseline treatments:
			• Ranibizumab 0.2mg: 23/74 (31.1%)
			Of these:
			  • 7 had laser therapy between days 1 and 29 (after initial ranibizumab)
			  • 4 had laser therapy between days 30 and 169
			  • 12 had ranibizumab re-treatment between days 30 and 169
			• Ranibizumab 0.1mg: 24/77 (31.2%)
			Of these[48]:
			  • 6 had laser therapy between days 1 and 29
			  • 4 had laser therapy between days 30 and 169
			  • 12 had ranibizumab re-treatment between days 30 and 169
			• Laser therapy: 10/74 (13.5%)[49]
			Of these:
				Patients were randomised using computer interactive response technology with stratification for disease zone and geographical region.
				
				There were some differences between the groups at baseline. It is not clear if these differences were likely to influence the study results.
				
				It would not have been practical to blind patients or clinicians to the treatment groups due to the differences in delivery methods. It is possible that the lack of blinding may introduce a potential bias for self-reported measures. However, it is unlikely to impact the objective outcomes reported. Outcome assessors were not blinded to treatment assignment although this would have been possible.
				
				Infants could receive additional treatments. The study authors stated that rules for additional

[46] Number of eyes treated taken from detail provided in Fleck et al 2022
[48] The figures cited are as reported in the paper. This states that 24 infants received additional treatments, however, the breakdown of additional treatments received only accounts for 22 infants
[49] The 4 infants in the laser therapy group who had additional treatment with ranibizumab between days 30 and 169 are classed as 'retreatment' rather than 'treatment failure' according to the definitions provided in the PICO document

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
December 2015 to June 2017	Zone I, stage 1+: 0% Zone I, stage 2+: 4.1% Zone I, stage 3: 4.1% Zone I, stage 3+: 16.2% Zone II, stage 2+: 0% Zone II, stage 3: 0% Zone II, stage 3+: 62.2% Aggressive posterior ROP: 13.5% *Ranibizumab 0.1mg* Male: 48% Gestational age in weeks (median, range): 26 (23 to 32) Birth weight g (mean ± SD): 886 ± 299 Postmenstrual age at treatment in weeks (median, range): 36.9 (31.9 to 54.9) Zone I, stage 1+: 1.3% Zone I, stage 2+: 1.3% Zone I, stage 3: 5.2% Zone I, stage 3+: 18.2% Zone II, stage 2+: 0% Zone II, stage 3: 1.3% Zone II, stage 3+: 58.4% Aggressive posterior ROP: 13.0% *Laser therapy* Male: 50% Gestational age in weeks (median, range): 26 (23 to 32)		• 1 had additional laser therapy between days 1 and 29 • 9 had ranibizumab between days 1 and 29 The laser therapy additional treatment numbers do not include 11 patients who received laser therapy to skip lesions before day 11 No statistical comparison between groups **Retreatment** 4/74 (5.4%) infants in the laser therapy group had an additional treatment with ranibizumab between days 30 and 169 **Development of infection** Number (%) with endophthalmitis • Ranibizumab 0.2mg: 0/73 (0%) • Ranibizumab 0.1mg: 1/76 (1.3%) • Laser therapy: 0/69 (0%) No statistical comparison between groups **Safety** Number (%) of deaths • Ranibizumab 0.2mg: 4/74 (5.4%) • Ranibizumab 0.1mg: 4/77 (5.2%) • Laser therapy: 4/74 (5.4%) No statistical comparison between groups *Serious ocular adverse events:* Number (%) of patients with a serious ocular adverse event: • Ranibizumab 0.2mg: 4/73 (5.5%) • Ranibizumab 0.1mg: 1/76 (1.3%)	treatments were set at a low threshold to minimise the risk of visual impairment and that decisions on retreatment were made on an individual basis and clinician preference for one treatment could lead to biased decisions to re-treat. Of the 225 infants enrolled in the RCT, 218 received baseline treatment and 201 (89%) completed the study. Of the 7 infants who did not receive a baseline treatment, 5 were randomised to laser therapy and 1 each to ranibizumab 0.2mg and 0.1mg respectively. The 17 infants who did not complete follow-up included 12 infants who died; 4 from each of the 3 groups. The authors stated that care was provided by clinicians from a wide range of settings and experience and no training was provided in the use of fundoscopy to determine the primary outcome. The authors also noted that only 86% of centres had access to retinal photography. The initial power calculation stated that at least 80 evaluable

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Birth weight g (mean ± SD): 831 ± 284 Postmenstrual age at treatment in weeks (median, range): 36.6 (30.6 to 55.3) Zone I, stage 1+: 2.7% Zone I, stage 2+: 6.8% Zone I, stage 3: 1.4% Zone I, stage 3+: 14.9% Zone II, stage 2+: 1.4% Zone II, stage 3: 0% Zone II, stage 3+: 59.5% Aggressive posterior ROP: 13.5% The authors reported that gestational age was slightly lower in the ranibizumab 0.2mg group than the other groups. The figures also suggest that mean birth weight was lower in the ranibizumab 0.2mg group The authors stated that "most other baseline characteristics were well balanced between study groups"		• Laser therapy: 4/69 (5.8%) No statistical comparison between groups Serious ocular adverse events were ROP (n=6), cataract (n=1), nystagmus[50] (n=1), conjunctivitis (n=1), endophthalmitis (n=1)[51], eye disorder (n=1)), orbital infection (n=1) *Ocular adverse events:* Number (%) of patients with any ocular adverse event: • Ranibizumab 0.2mg: 22/73 (30.1%) • Ranibizumab 0.1mg: 31/76 (40.8%) • Laser therapy: 23/69 (33.3%) No statistical comparison between groups The most common ocular adverse events (n>5) were conjunctival haemorrhage, retinal haemorrhage, ROP and conjunctivitis *Non-ocular serious adverse events:* Number (%) of patients with a serious non-ocular adverse event: • Ranibizumab 0.2mg: 24/73 (32.9%) • Ranibizumab 0.1mg: 24/76 (31.6%) • Laser therapy: 22/69 (31.9%) No statistical comparison between groups The most common serious non-ocular adverse events (n>5) were pneumonia, bronchiolitis and bronchopulmonary dysplasia *Non-ocular adverse events:*	patients per treatment group (100 enrolled per group with an assumed 20% drop out rate) would provide more than 90% power to show superiority of ranibizumab 0.2mg compared to laser therapy. However, this target was later revised due to slow enrolment and recruitment challenges to 48 evaluable patients per treatment group (60 enrolled per group) with more than 80% power to show superiority. The power of the study was therefore reduced from what was originally intended. Statistical analysis of the primary outcome was intention-to-treat. The primary outcome reported by the study was a composite outcome for treatment success (defined by survival without active ROP, unfavourable structural outcomes or the need for a treatment modality other than that assigned). This composite outcome was not specified as an outcome of interest for this review. Although appropriate statistical analysis was undertaken for the primary

[50] This is also reported under the sight impairment/ severe sight impairment outcome
[51] This is also reported under the development of infection outcome

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

	Categorisation of ROP was described as 'similarly distributed across treatment groups at baseline"		Number (%) of patients with any non-ocular adverse event:
			• Ranibizumab 0.2mg: 62/73 (84.9%)
			• Ranibizumab 0.1mg: 62/76 (81.6%)
			• Laser therapy: 53/69 (76.8%)
			No statistical comparison between groups
			
			The most common non-ocular adverse events (n>10) were pyrexia, dermatitis diaper, nasopharyngitis, upper respiratory tract infection, anaemia, gastro oesophageal reflux disease, pneumonia, bronchopulmonary dysplasia and vomiting
			
			Serum plasma VEGF levels
			Serum ranibizumab pg/mL (median, IQR):
			• Ranibizumab 0.2mg
			  • Day 1 (n=49): 7,820 (2,000 to 23,200)
			  • Day 15 (n=45): 4,440 (2,450 to 8,130)
			  • Day 29 (n=31): 1,070 (705 to 1,730)
			• Ranibizumab 0.1mg
			  • Day 1 (n=46): 4,350 (382 to 12,100)
			  • Day 15 (n=36): 3,400 (2,515 to 5,215)
			  • Day 29 (n=24): 566 (303 to 1,060)
			N/A for laser therapy
			No statistical comparison over time
			
			Plasma VEGF pg/mL (median, IQR):
			• Ranibizumab 0.2mg
			  • Day 1 (n=17): 136 (78 to 414)
			  • Day 15 (n=21): 71.8 (54 to 124)
			  • Day 29 (n=13): 89 (74 to 105)
			• Ranibizumab 0.1mg
			  • Day 1 (n=21): 130 (81 to 388)
			  • Day 15 (n=26): 67 (37 to 156)
				outcome, the authors stated that because a statistically significant difference was not observed for the primary outcome, other significance testing was not undertaken.
				
				The study duration was 24 weeks. Therefore all the additional treatments received by patients in the ranibizumab groups are classed as treatment failure rather than retreatment (according to the definitions provided in the PICO document). However, the distinction between the definitions for treatment failure and retreatment for laser therapy in the PICO is based on whether this took place within or after 4 weeks from the initial treatment. Therefore, additional treatments in the laser group that took place after day 30 have been classed as retreatment.
				
				Results comparing the 2 doses of ranibizumab were not extracted as this comparison is out of scope for this review.
				
				Prespecified subgroup analysis was reported for the primary outcome (treatment success). However, subgroup analysis was

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Day 29 (n=18): 140 (97 to 209) • Laser therapy • Day 1 (n=46): 136 (79 to 288) • Day 15 (n=44): 86.1 (56 to 230) • Day 29 (n=30): 123 (63 to 181) No statistical comparison between groups or over time	not reported for the outcomes of interest for this review. The study was conducted in 87 centres in 26 countries. Three of the 87 centres were in the UK with five of the 225 patients randomised from these UK centres. The authors stated that 40% of the randomised infants came from a geographical region with infant mortality of at least five per 1,000 births and 60% from a geographical region with infant mortality of less than five per 1,000 births, with the UK being in this latter group. **Source of funding:** The study was funded by Novartis Pharma AG. The authors stated that the funder of the study had full access to data collection, analysis and interpretation and was involved in the writing of the manuscript and the decision to submit
Zhang G, Yang M, Zeng J, Vakros G, Su K, Chen M, Li H, Tian R, Li N, Tang S, He H, Tan W, Song X, Zhuang R. Comparison of intravitreal injection of ranibizumab versus laser therapy for zone II	Preterm infants with Zone II ROP **Inclusion criteria** Preterm infants (birth weight <2,000g or birth weight ≥2,000g but with severe systemic disorders) were screened.	**Intervention** Intravitreal injection of ranibizumab under topical anaesthesia as a single dose of 0.3mg in 0.03mL An ophthalmic antibiotic eye drop	Patients were examined 1 and 4 weeks after treatment and then monthly for at least 6 months. Mean ± SD (range) follow-up (weeks): • Ranibizumab: 49.94 ± 14.67 (range 27.71 to 78.71). • Laser therapy: 54.03 ± 12.40 (range 23.86 to 77.86) p=0.37	This study was appraised using the JBI checklist for RCTs: 1. Yes 2. Yes 3. Yes 4. No 5. No 6. Unclear

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
treatment-requiring retinopathy of prematurity. Retina. 2017;37(4):710-7. **Study location** Single-centre, China **Study type** RCT **Study aim** To compare the efficacy of ranibizumab and laser therapy for ROP in Zone II **Study dates** January to December 2014	Infants with binocular Zone II treatment-requiring ROP (i.e. ROP with Stage 2+ or 3+ in Zone II) were included **Exclusion criteria** Preterm infants with ROP in Zone I, Stage 4 or Stage 5 ROP and aggressive posterior ROP in either eye **Total sample size** n=50 preterm infants (100 eyes) Ranibizumab: n=25 (50 eyes) Laser therapy: n=25 (50 eyes) **Baseline characteristics** *Ranibizumab* Male: 56.0% Gestational age in weeks (mean ± SD): 28.96 ± 1.59 Birth weight kg (mean ± SD): 1.22 ± 0.32 *Laser therapy* Male/ female: 56.0% Gestational age in weeks (mean ± SD): 28.27 ± 1.84	was prescribed for the treated eye to begin immediately and continued 4 times a day for 7 days **Comparison** Laser photocoagulation performed under sedation Topical steroid and cycloplegicmydriatic were administered for 1 week after photocoagulation Any eyes that developed recurrence of ROP underwent crossover treatment	**Critical outcomes** **Unfavourable structural retinal outcomes** The authors stated that no infant had retinal detachment at last follow-up **Important outcomes** **Treatment failure** Number (%) of patients who received a second treatment due to recurrence: • Ranibizumab: 11/25 (44.0%) Time to recurrence ranged from 4 to 13 weeks • Laser therapy: 1/25 (4.0%) Time to recurrence was 1 week No statistical comparison for the number of infants receiving a second treatment reported **Development of infection** The authors stated that no infant had endophthalmitis at last follow-up **Safety** The authors stated that no infant had anterior segment ischemia, pupillary membrane, lens opacity or vitreous haemorrhage at last follow-up	7. No 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes **Other comments** This RCT compared infants randomised to receive ranibizumab or laser therapy. A computer-generated randomisation schedule was applied. No detail of any power calculation was reported. It would not have been practical to blind patients or clinicians to the treatment groups due to the differences in delivery methods. However, it is unlikely to impact the objective outcomes reported. It is not stated whether outcome assessors were blinded to treatment assignment. Some patients received a crossover treatment. More infants in the ranibizumab group received a crossover treatment although the difference between groups was not statistically compared and the importance of

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Birth weight kg (mean ± SD): 1.06 ± 0.24 Groups were similar at baseline for gestational age, birth weight, sex ratio, proportion of single or twin births and delivery methods			this to the outcomes of interest to this review was not clear. All patients were included in the analyses reported. Although the RCT included appropriate statistical analysis, no statistical analysis was conducted for the outcomes of interest for this review. The study was conducted in 1 centre in China over a 1 year period. The generalisability of the results to the NHS in England is unclear. **Source of funding** The study was supported by two grants from Shenzhen Science and Technology Innovation Committee. It is stated that none of the authors had any financial/ conflicting interests to disclose

Abbreviations
BEAT-ROP: Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity; CI: Confidence intervals; CVFQ; Children's Visual Function Questionnaire; ETROP: Early Treatment for Retinopathy of Prematurity; g: Grams; IQR: inter quartile range; kg: Kilogram; mg: Milligram; ml: Millilitres; N/A: Not applicable; OR: Odds ratio; pg/mL: Picogram/millilitre; PICO: Population, intervention, comparator, outcome; PMA: Postmenstrual age; RCT: Randomised controlled trial; ROP: Retinopathy of prematurity; SD: Standard deviation; VEGF: Vascular endothelial growth factor

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blinded to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisations, parallel groups) accounted for in the conduct and analysis of the trial

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

Appendix G GRADE profiles

In preterm infants diagnosed with ROP, what is the clinical effectiveness and safety of ranibizumab as first line drug treatment compared with standard of care?

For abbreviations and footnotes see end of tables.

Table 2. Ranibizumab compared to laser therapy (retinal photocoagulation)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Ranibizumab	Laser therapy	Result		
Unfavourable structural retinal outcomes (2 RCTs, 1 RCT extension study and 3 cohort studies)									
Unfavourable structural retinal outcomes (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	0.2mg: 1/74 (1.4%) 0.1mg: 5/77 (6.5%)	7/74 (9.5%)	No statistical comparison between groups	Critical	Low
Retinal detachment (number, %) at mean ± SD 49.94 ± 14.67 (ranibizumab) and 54.03 ± 12.40 (laser therapy) weeks follow-up (benefit indicated by lower score)									
1 RCT Zhang et al 2017	Serious limitations[2]	No serious indirectness	Not applicable	Serious imprecision[3]	0/25 (0%)	0/25 (0%)	No cases of retinal detachment at last follow-up	Critical	Low
Unfavourable anatomical outcomes (number, %) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 20.68 ± 6.89 (laser therapy) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Very serious limitations[4]	No serious indirectness	Not applicable	Serious imprecision[5]	0/22 (0%)	1/57 (1.8%)	No statistical comparison between groups	Critical	Very low
Structural abnormalities (number, %) present at evaluation at age 20-28 months (benefit indicated by lower score)									
1 RCT extension	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	0.2mg: 1/56 (1.8%)	4/44 (9.1%)	No statistically significant difference between groups in	Critical	Low

study RAINBOW Marlow et al 2021					0.1mg: 1/51 (2.0%)		likelihood of having no structural abnormality: • Ranibizumab 0.2mg vs laser therapy: OR 5.68 (95%CI 0.60 to 54), p=0.10 • Ranibizumab 0.1mg vs laser therapy: OR 4.82 (95%CI 0.52 to 45), p=0.14		
Retinal detachment (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Not calculable	1/153 eyes (0.7%)	8/161 eyes (5.0%)	Statistically significantly fewer cases with ranibizumab (p=0.037)	Critical	Very low
Temporal macular dragging (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Not calculable	1/153 eyes (0.7%)	7/161 eyes (4.3%)	Statistically significantly fewer cases with ranibizumab (p=0.039)	Critical	Very low
Progression to retinal detachment (number of eyes, %) at mean ± SD 197.3 ± 110 weeks follow-up (benefit indicated by lower score)									
1 retrospective cohort study Ling et al 2020	Serious limitations[8]	No serious indirectness	Not applicable	Not calculable	1/48 eyes (2.1%)	3/61 eyes (4.9%)	No statistically significant differences between groups (p=0.2701)[a]	Critical	Very low
High myopia (1 RCT extension study and 1 cohort study)									
Patients with high myopia (%) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 20.68 ± 6.89 (laser therapy) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Serious limitations[7]	No serious indirectness	Not applicable	Not calculable	13.6%	14%	No statistically significant differences between groups (p=0.979)[a]	Critical	Very low
Prevalence of high myopia per eye (number of eyes, %) present at evaluation at age 20-28 months (benefit indicated by lower score)									
1 RCT extension study RAINBOW	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	0.2mg: 5/110 eyes (4.5%) 0.1mg:	16/82 eyes (19.5%)	Ranibizumab 0.2mg vs laser therapy: OR 0.19 (95%CI 0.05 to 0.69), p=0.012	Critical	Low

Marlow et al 2021					8/98 eyes (8.2%)		Ranibizumab 0.1mg vs laser therapy: OR 0.44 (95%CI 0.14 to 1.32), p=0.14		
High myopia in at least one eye (number, %) present at evaluation at age 20-28 months (benefit indicated by lower score)									
1 RCT extension study RAINBOW Marlow et al 2021	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	0.2mg[b]: 4/55 (7.3%)	14/41 (34.1%)	OR 0.15 (95%CI 0.05 to 0.50), p=0.0021	Critical	Low
Sight impairment/ severe sight impairment (1 RCT, 1 RCT extension study and 1 cohort study)									
Nystagmus (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Serious imprecision[3]	0.2mg: 1/73 (1.4%) 0.1mg: 0/76 (0%)	0/69 (0%)	No statistical comparison between groups	Critical	Very low
Nystagmus (number, %) at evaluation at age 20-28 months (benefit indicated by lower score)									
1 RCT extension study RAINBOW Marlow et al 2021	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 2/55 (3.6%) 0.1mg: 3/50 (6.0%)	5/41 (12.2%)	No statistical comparison between groups	Critical	Low
Strabismus (number, %) at evaluation at age 20-28 months (benefit indicated by lower score)									
1 RCT extension study RAINBOW Marlow et al 2021	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 11/55 (20.0%) 0.1mg: 12/49 (24.5%)	13/41 (31.7%)	No statistical comparison between groups	Critical	Low
Abnormal fixation (number, %) at evaluation at age 20-28 months (benefit indicated by lower score)									
1 RCT extension	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 1/55 (1.8%)	2/44 (14.5%)	No statistical comparison between groups	Critical	Low

study RAINBOW Marlow et al 2021					0.1mg: 8/52 (15.4%)				
Abnormal pupil reaction (number, %) at evaluation at age 20-28 months (benefit indicated by lower score)									
1 RCT extension study RAINBOW Marlow et al 2021	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 0/55 (0%) 0.1mg: 3/52 (6.0%)	1/42 (2.4%)	No statistical comparison between groups	Critical	Low
Strabismus operation (number of eyes, %) at mean ± SD 36.3 ± 31.9 months (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Not calculable	21/153 eyes (13.7%)	26/161 eyes (16.1%)	No statistically significant difference between groups (p=0.636)	Critical	Very low
Treatment failure (2 RCTs and 4 cohort studies)									
Patients receiving additional treatments (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 23/74 (31.1%) 0.1mg: 24/77 (31.2%)	10/74 (13.5%)	Additional treatments for the ranibizumab group occurred between day 1 and day 169 after the initial treatment Additional treatments for the laser therapy group occurred between day 1 and day 29 No statistical comparison between groups	Important	Low
Recurrence of ROP requiring any additional treatment (number of eyes, %) at follow-up of up to 6 months (benefit indicated by lower score)									
1 retrospective cohort study Chmielarz-Czarnocińska et al 2021	Very serious limitations[4]	No serious indirectness	Not applicable	Serious imprecision [10]	80/120 eyes (66.7%)	0/226 eyes (0%)	Time to first retreatment 51 days (7.3 weeks) to 178 days (25.4 weeks). Time to retreatment not separately reported for treatment groups[c]	Important	Very low

							No statistical comparison between groups		
Second treatment due to recurrence (number, %) at mean ± SD 49.94 ± 14.67 (ranibizumab) and 54.03 ± 12.40 (laser therapy) weeks follow-up (benefit indicated by lower score)									
1 RCT Zhang et al 2017	Serious limitations [11]	No serious indirectness	Not applicable	Not calculable	11/25 (44.0%)	1/25 (4.0%)	Ranibizumab time to recurrence: 4 to 13 weeks Laser therapy time to recurrence: 1 week No statistical comparison between groups	Important	Moderate
Retreatment (number, %) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 20.68 ± 6.89 (laser therapy) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Serious limitations[7]	No serious indirectness	Not applicable	Serious imprecision [10]	3/22 (13.6%)	0/57 (0%)	Ranibizumab time to retreatment (mean ± SD): 8.75 ± 1.5 weeks No statistically significant differences between groups (p=0.098)[a]	Important	Very low
Recurrence of ROP requiring any additional treatment (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Not calculable	15/153 eyes (9.8%)	22/161 eyes (13.7%)	Ranibizumab mean time to retreatment: 5.7 weeks Laser therapy mean time to retreatment: 2.3 weeks No statistically significant difference between groups (p=0.196)	Important	Very low
Recurrence of ROP requiring retreatment (number of eyes, %) at mean ± SD 197.3 ± 110 weeks follow-up (benefit indicated by lower score)									
1 retrospective cohort study Ling et al 2020	Serious limitations[8]	No serious indirectness	Not applicable	Not calculable	10/48 eyes (20.8%)	11/61 eyes (18.0%)	Ranibizumab time to retreatment (mean ± SD): 8.3 ± 1.6 weeks Laser therapy time to retreatment (mean ± SD): 3.6 ± 1.4 weeks[d] No statistically significant differences between groups (p=0.0528)[a]	Important	Very low

Quality of life (1 RCT extension study)									
Children's Visual Function Questionnaire composite score, mean (95%CI) at evaluation at age 20-28 months (benefit indicated by higher score)									
1 RCT extension study RAINBOW Marlow et al 2021	Very serious limitations [12]	No serious indirectness	Not applicable	Not calculable	0.2mg: 54 0.1mg: 50	37	Composite vision-related quality of life score: • Ranibizumab 0.2mg: 84 (95%CI 80 to 88) • Ranibizumab 0.1mg: 79 (95%CI 75 to 83) • Laser therapy: 77 (95%CI 72 to 83) Ranibizumab 0.2mg vs laser: p=0.063 Ranibizumab 0.1mg vs laser: p>0.05	Important	Low
Mullen Scales of Early Learning, median (IQR) at evaluation at age 20-28 months (benefit indicated by higher score)									
1 RCT extension study RAINBOW Marlow et al 2021	Very serious limitations [12]	No serious indirectness	Not applicable	Not calculable	0.2mg: 56 0.1mg: 52	43	Visual reception T-score: • Ranibizumab 0.2mg: 40 (29 to 52) • Ranibizumab 0.1mg: 38 (25 to 49) • Laser therapy: 40 (20 to 49) Receptive language T-score: • Ranibizumab 0.2mg: 44 (36 to 50) • Ranibizumab 0.1mg: 40 (27 to 49) • Laser therapy: 40 (27 to 50) Expressive language T-score: • Ranibizumab 0.2mg: 36 (30 to 44) • Ranibizumab 0.1mg: 30 (25 to 41) • Laser therapy: 33 (22 to 46)	Important	Low

							No statistical comparison between groups		
Retreatment (1 RCT and extension study and 1 cohort study)									
Recurrence of ROP requiring any additional treatment (number of eyes, %) at follow-up of up to 6 months (benefit indicated by lower score)									
1 retrospective cohort study Chmielarz-Czarnocińska et al 2021	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	Not reported for ranibizumab	46/226 eyes (20.4%)	Time to first retreatment 51 days (7.3 weeks) to 178 days (25.4 weeks)	Important	Very low
Retreatment during the initial trial (up to 24 weeks follow-up) or extension study (>24 weeks to approximately 2 years after initial treatment) (number, %) (benefit indicated by lower score)									
1 RCT and extension study RAINBOW Stahl et al 2019 Marlow et al 2021	Very serious limitations[9]	No serious indirectness	Not applicable	Serious imprecision [5]	0.2mg: 0/56 (0%) 0.1mg: 1/53 (1.9%)	4/74 (5.4%)	No statistical comparison between groups	Important	Very low
Development of infection (2 RCTs and 1 cohort studies)									
Endophthalmitis (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Serious imprecision [3]	0.2mg: 0/73 (0%) 0.1mg: 1/76 (1.3%)	0/69 (0%)	No statistical comparison between groups	Important	Very low
Endophthalmitis (number, %) at mean ± SD 49.94 ± 14.67 (ranibizumab) and 54.03 ± 12.40 (laser therapy) weeks follow-up (benefit indicated by lower score)									
1 RCT Zhang et al 2017	Serious limitations[2]	No serious indirectness	Not applicable	Serious imprecision[3]	0/25 (0%)	0/25 (0%)	No cases of endophthalmitis at last follow-up	Important	Low
Endophthalmitis (number, %) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 20.68 ± 6.89 (laser therapy) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study	Serious limitations[7]	No serious indirectness	Not applicable	Serious imprecision[3]	0/22 (0%)	0/57 (0%)	No cases of endophthalmitis at last follow-up	Important	Very low

Gunay et al 2017									
Safety (2 RCTs, 1 RCT extension study and 2 cohort studies)									
Plasma VEGF pg/mL (median, IQR) up to 29 days follow-up (benefit indicated by lower score)									

1 RCT
RAINBOW
 	
Stahl et al 2019
	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 21
					
					0.1mg: 26
						46	• Ranibizumab 0.2mg
							  • Day 1 (n=17): 136 (78 to 414)
							  • Day 15 (n=21): 71.8 (54 to 124)
							  • Day 29 (n=13): 89 (74 to 105)
							• Ranibizumab 0.1mg
							  • Day 1 (n=21): 130 (81 to 388)
							  • Day 15 (n=26): 67 (37 to 156)
							  • Day 29 (n=18): 140 (97 to 209)
							• Laser therapy
							  • Day 1 (n=46): 136 (79 to 288)
							  • Day 15 (n=44): 86.1 (56 to 230)
							  • Day 29 (n=30): 123 (63 to 181)
							No statistical comparison between groups or over time
								Important	Low

Serum ranibizumab pg/mL (median, IQR) up to 29 days follow-up (benefit indicated by lower score)									

1 RCT
RAINBOW
 	
Stahl et al 2019
	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 49
					
					0.1mg: 46
						Outcome not applicable for laser therapy	• Ranibizumab 0.2mg
							  • Day 1 (n=49): 7,820 (2,000 to 23,200)
							  • Day 15 (n=45): 4,440 (2,450 to 8,130)
							  • Day 29 (n=31): 1,070 (705 to 1,730)
							• Ranibizumab 0.1mg
							  • Day 1 (n=46): 4,350 (382 to 12,100)
							  • Day 15 (n=36): 3,400 (2,515 to 5,215)
								Important	Low

							• Day 29 (n=24): 566 (303 to 1,060) No statistical comparison over time		
Deaths (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 4/74 (5.4%) 0.1mg: 4/77 (5.2%)	4/74 (5.4%)	No statistical comparison between groups	Important	Low
Serious ocular adverse events (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 4/73 (5.5%) 0.1mg: 1/76 (1.3%)	4/69 (5.8%)	No statistical comparison between groups	Important	Low
Any ocular adverse events (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 22/73 (30.1%) 0.1mg: 31/76 (40.8%)	23/69 (33.3%)	No statistical comparison between groups	Important	Low
Serious non-ocular adverse events (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 24/73 (32.9%) 0.1mg: 24/76 (31.6%)	22/69 (31.9%)	No statistical comparison between groups	Important	Low
Any non-ocular adverse events (number, %) up to 24 weeks follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Stahl et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 62/73 (84.9%) 0.1mg: 62/76 (81.6%)	53/69 (76.8%)	No statistical comparison between groups	Important	Low

Specified adverse events (number, %) at mean ± SD 49.94 ± 14.67 (ranibizumab) and 54.03 ± 12.40 (laser therapy) weeks follow-up (benefit indicated by lower score)									
1 RCT Zhang et al 2017	Serious limitations[2]	No serious indirectness	Not applicable	Serious imprecision[3]	0/25 (0%)	0/25 (0%)	The authors stated that no infant had anterior segment ischemia, pupillary membrane, lens opacity or vitreous haemorrhage at last follow-up	Important	Low
Major ocular complications (number, %) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 20.68 ± 6.89 (laser therapy) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Serious limitations[7]	No serious indirectness	Not applicable	Serious imprecision[3]	0/22 (0%)	0/57 (0%)	No cases of major ocular complications, including iatrogenic cataract or intraocular haemorrhage, at last follow-up	Important	Very low
Adverse ocular events (number) at up to 2 years follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Marlow et al 2021	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	0.2mg: 74 0.1mg: 77	74	Ranibizumab 0.2mg: 2 Ranibizumab 0.1mg: 6[e] Laser therapy: 3 Number of patients experiencing an adverse event not stated No statistical comparison between groups	Important	Low
Non-ocular serious adverse events related to study intervention (number, %) at up to 2 years follow-up (benefit indicated by lower score)									
1 RCT RAINBOW Marlow et al 2021	Very serious limitations[6]	No serious indirectness	Not applicable	Serious imprecision[3]	0.2mg: 0/74 (0%) 0.1mg: 0/77 (0%)	0/74 (0%)	No cases of non-ocular serious adverse events related to the study intervention at last follow-up	Important	Very low
Vitreous haemorrhage (major complication) (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Not calculable	2/153 eyes (1.3%)	1/161 eyes (0.6%)	No statistically significant difference between groups (p=0.614)	Important	Very low
Cataract (major complication) (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study	Serious limitations[7]	No serious indirectness	Not applicable	Not calculable	1/153 eyes (0.7%)	1/161 eyes (0.6%)	No statistically significant difference between groups (p=0.738)	Important	Very low

Kang et al 2019									
Pale disc without known neurologic deficits (major complication) (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Not calculable	8/153 eyes (5.2%)	5/161 eyes (3.1%)	No statistically significant difference between groups (p=0.404)	Important	Very low
Glaucoma (major complication) (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Serious imprecision[5]	0/153 eyes (0%)	2/161 eyes (1.2%)	No statistically significant difference between groups (p=0.499)	Important	Very low
Deaths or major systematic complications (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Serious imprecision[3]	0/153 eyes (0%)	0/161 eyes (0%)	No cases of deaths or major systemic complications at last follow-up	Important	Very low
Adverse neurodevelopmental outcomes (number of eyes, %) at mean ± SD 36.3 ± 31.9 months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2019	Serious limitations[7]	No serious indirectness	Not applicable	Serious imprecision[3]	0/153 eyes (0%)	0/161 eyes (0%)	No cases of adverse neurodevelopmental outcomes at last follow-up	Important	Very low

Abbreviations

CI: Confidence intervals; IQR: Interquartile range; mg: Milligram; OR: Odds ratio; pg/mL: Picogram/millilitre; RCT: Randomised controlled trial; ROP: Retinopathy of prematurity; SD: Standard deviation

1. Risk of bias. Very serious limitations due to uncertainty about differences between the groups at baseline and in the way the two groups were treated, incomplete follow-up, uncertainty about whether the outcome was measured in a reliable way and lack of statistical analysis
2. Risk of bias. Serious limitations due to differences in the way the two groups were treated
3. Imprecision: Serious imprecision due to 0 events in both arms
4. Risk of bias. Very serious limitations due to lack of clarity about the similarity between the groups at baseline, lack of adjustment for potential confounding factors, uncertainty about whether follow-up was complete and lack of statistical analysis between groups
5. Imprecision: Serious imprecision due to 0 events in the intervention arm

6. Risk of bias. Very serious limitations due to uncertainty about differences between the groups at baseline and in the way the two groups were treated and incomplete follow-up
7. Risk of bias. Serious limitations due to lack of clarity about the similarity between the groups at baseline, lack of adjustment for potential confounding factors and uncertainty about whether follow-up was complete
8. Risk of bias. Serious limitations due to lack of adjustment for potential confounding factors and incomplete follow-up
9. Risk of bias. Very serious limitations due to uncertainty about differences between the groups at baseline and in the way the two groups were treated, incomplete follow-up and lack of statistical analysis
10. Imprecision: Serious imprecision due to 0 events in the comparator arm
11. Risk of bias. Serious limitations due to differences in the way the two groups were treated and lack of statistical analysis
12. Risk of bias. Very serious limitations due to uncertainty about differences between the groups at baseline and in the way the two groups were treated, lack of blinding for this subjective outcome and incomplete follow-up

a The statistical comparison reported was between ranibizumab, laser therapy and bevacizumab
b Result not reported for ranibizumab 0.1mg
c The lower and upper end of the time to retreatment range suggests that most of the additional treatments received by the ranibizumab group fall within the PICO definition of treatment failure for ranibizumab (i.e. within 24 weeks) and all the additional treatments received by the laser therapy group fall within the PICO definition of retreatment for laser therapy (i.e. >4 weeks)
d The mean and SD time to recurrence for laser therapy suggests that some infants received retreatment post 4 weeks but this number is not reported
e This includes 2 cases of retinal detachment which may have also been included under the structural abnormalities outcome for this study

Table 3. Ranibizumab compared to bevacizumab

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Ranibizumab	Bevacizumab	Result		
Unfavourable structural retinal outcomes (3 cohort studies)									
Retinal detachment (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[2]	0/52 eyes (0%)	1/101 eyes (1.0%)	No statistically significant difference between groups (p=0.660)	Critical	Very low
Temporal macular dragging (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[3]	1/52 eyes[a] (1.9%)	0/101 eyes (0%)	No statistically significant difference between groups (p=0.340)	Critical	Very low
Unfavourable anatomical outcomes (number, %) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 19.40 ± 6.43 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[4]	0/22 (0%)	0/55 (0%)	No cases of unfavourable anatomical outcomes observed	Critical	Very low
Progression to retinal detachment (number of eyes, %) at mean ± SD 197.3 ± 110 weeks follow-up (benefit indicated by lower score)									
1 retrospective cohort study Ling et al 2020	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	1/48 eyes (2.1%)	2/231 eyes (0.9%)	No statistically significant differences between groups (p=0.2701)[b]	Critical	Very low
High myopia (1 cohort study)									
High myopia (%) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 19.40 ± 6.43 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	13.6%	12.7%	No statistically significant differences between groups (p=0.979)[b]	Critical	Very low

Sight impairment/ severe sight impairment (1 cohort study)									
Strabismus operations (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[2]	0/52 eyes (0%)	21/101 eyes (20.8%)	Statistically significantly lower with ranibizumab (p<0.001)	Critical	Very low
Treatment failure (3 cohort studies)									
Recurrence of ROP requiring any additional treatment (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	7/52 eyes (13.5%)	8/101 eyes (7.9%)	Time to retreatment not reported[c] No statistical comparison between groups	Important	Very low
Eyes requiring additional anti-VEGF treatment (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	7/52 eyes (13.5%)	4/101 eyes (4.0%)	Time to retreatment not reported[c] Statistically significantly higher with ranibizumab (p=0.037)	Important	Very low
Retreatment (number, %) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 19.40 ± 6.43 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	3/22 (13.6%)	3/55 (5.5%)	Ranibizumab time to retreatment (mean ± SD): 8.75 ± 1.5 weeks Bevacizumab time to retreatment (mean ± SD): 14 ± 2.65 weeks No statistically significant differences between groups (p=0.098)[b]	Important	Very low
Recurrence of ROP requiring retreatment (number of eyes, %) at mean ± SD 197.3 ± 110 weeks follow-up (benefit indicated by lower score)									
1 retrospective cohort study Ling et al 2020	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	10/48 eyes (20.8%)	23/231 eyes (10.0%)	Ranibizumab time to recurrence (mean ± SD): 8.3 ± 1.6 weeks Bevacizumab time to recurrence (mean ± SD): 8.8 ± 3.9 weeks	Important	Very low

							No statistically significant differences between groups (p=0.0528)[b]		
Development of infection (1 cohort study)									
Endophthalmitis (number, %) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 19.40 ± 6.43 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[4]	0/22 (0%)	0/55 (0%)	No cases of endophthalmitis at last follow-up	Important	Very low
Safety (2 cohort studies)									
Vitreous haemorrhage (major complication) (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	1/52 eyes (1.9%)	1/101 eyes (1.0%)	No statistically significant difference between groups (p=0.566)	Important	Very low
Cataract (major complication) (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[2]	0/52 eyes (0%)	1/101 eyes (1.0%)	No statistically significant difference between groups (p=0.660)	Important	Very low
Pale disc without known neurologic deficits (major complication) (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	4/52 eyes (7.7%)	4/101 eyes (4.0%)	No statistically significant difference between groups (p=0.445)	Important	Very low
Glaucoma (major complication) (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[4]	0/52 eyes (0%)	0/101 eyes (0%)	No cases of glaucoma at last follow-up	Important	Very low

Deaths or major systematic complications (number of eyes, %) at mean ± SD 13.9 ± 12.5 (ranibizumab) and 30.9 ± 18.4 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Kang et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[4]	0/52 eyes (0%)	0/101 eyes (0%)	No cases of deaths or major systemic complications at last follow-up	Important	Very low
Major ocular complications (number, %) at mean ± SD 18.96 ± 4.79 (ranibizumab) and 19.40 ± 6.43 (bevacizumab) months follow-up (benefit indicated by lower score)									
1 retrospective cohort study Gunay et al 2017	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[4]	0/22 (0%)	0/55 (0%)	No cases of major ocular complications, including iatrogenic cataract or intraocular haemorrhage, at last follow-up	Important	Very low

Abbreviations
ROP: Retinopathy of prematurity; SD: Standard deviation; VEGF: Vascular endothelial growth factor

1. Risk of bias. Serious limitations due to lack of clarity about the similarity between the groups at baseline, lack of adjustment for potential confounding factors and uncertainty about whether follow-up was complete
2. Imprecision: Serious imprecision due to 0 events in the intervention arm
3. Imprecision: Serious imprecision due to 0 events in the comparator arm
4. Imprecision: Serious imprecision due to 0 events in both arms
5. Risk of bias. Serious limitations due to lack of adjustment for potential confounding factors and incomplete follow-up
6. Risk of bias. Very serious limitations due to lack of clarity about the similarity between the groups at baseline, lack of adjustment for potential confounding factors, uncertainty about whether follow-up was complete and lack of statistical analysis

a There is a discrepancy in the paper about whether the one infant with temporal macular dragging received bevacizumab or ranibizumab. The result from the data table (rather than the text) is reported here
b The statistical comparison reported was between ranibizumab, laser therapy and bevacizumab
c These results are presented as treatment failure due to the absence of any evidence to confirm that retreatment was required after 24 weeks

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Comparative cohort study	An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

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